

**UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK**

UNITED STATES OF AMERICA; THE
COMMONWEALTHS OF
MASSACUSETTS AND VIRGINIA,
THE STATES OF CALIFORNIA,
DELAWARE, CONNECTICUT,
MARYLAND, COLORADO, FLORIDA,
GEORGIA, ILLINOIS, INDIANA,
HAWAII, LOUISIANA, MICHIGAN,
MONTANA, NEW HAMPSHIRE, NEW
MEXICO, NEW YORK, NEVADA,
TENNESSEE, NEW JERSEY, RHODE
ISLAND, OKLAHOMA, WISCONSIN,
NORTH CAROLINA, MINNESOTA
AND WASHINGTON, THE CITY OF
CHICAGO AND THE DISTRICT OF
COLUMBIA *ex rel.* ALLISON ZAYAS,

Plaintiff-Relator

v.

ASTRAZENECA
BIOPHARMACEUTICALS, INC.
ASTRAZENECA PLC,
ASTRAZENECA LP, and
ASTRAZENECA
PHARMACEUTICALS, LP

Defendants.

FILED IN CAMERA & UNDER SEAL

JURY TRIAL DEMANDED

CIVIL ACTION: 1:14-cv-01718-FB-SMG

COMPLAINT FOR VIOLATIONS OF THE FEDERAL
FALSE CLAIMS ACT [31 U.S.C. §3729 *et seq.*];
CALIFORNIA FALSE CLAIMS ACT [Cal. Gov. Code
§12650 *et seq.*]; DELAWARE FALSE CLAIMS &
REPORTING ACT [6 Del. C. §1201 *et seq.*]; DISTRICT
OF COLUMBIA PROCUREMENT REFORM
AMENDMENT ACT [D.C. Code Ann. §1-1188.14 *et seq.*];
FLORIDA FALSE CLAIMS ACT [Fla. Stat. Ann. §68.081
et seq.]; ILLINOIS WHISTLE BLOWER REWARD &
PROTECTION ACT [740 ILCS § 175 *et seq.*]; HAWAII
FALSE CLAIMS ACT [Haw. Rev. Stat. § 661-21(a)(3)]
MONTANA FALSE CLAIMS ACT; [Mont. Code Ann.
§17-410, Mont. Code Ann § 17-8-403]; INDIANA
FALSE CLAIMS ACT AND WHISTLEBLOWERS
PROTECTION ACT [Ind. Code Ann. §5-11-5.5-1-5-11-
5.5-18]; MICHIGAN MEDICAID FALSE CLAIMS ACT
[Mich. Comp. Laws § 400.603, 606 and 607]; NEW
HAMPSHIRE FALSE CLAIMS ACT [New Hamp. Stat.
167:61-b]; LOUISIANA FALSE CLAIMS ACT [La. Rev.
Stat. Ann. § 46:439.1 *et seq.*]; MASSACHUSETTS FALSE
CLAIMS ACT [Massachusetts Gen. Laws c.12 §5(A)];
NEW MEXICO MEDICAID FALSE CLAIMS ACT [N.M.
Stat. Ann. § 27-14-1-27-14-15]; NEVADA FALSE
CLAIMS ACT [Nev. Rev. Stat. Ann. §357.010 *et seq.*];
TENNESSEE MEDICAID FALSE CLAIMS ACT [Tenn.
Code Ann. §71-5-181 *et seq.*]; VIRGINIA FRAUD
AGAINST TAXPAYERS ACT [Va. Stat. Ch. 842, Art.
19.1, §8.01-216.1 *et seq.*]; GEORGIA STATE MEDICAID
ACT [Ga. Code 49-4-168 *et seq.*]; NEW YORK FALSE
CLAIMS ACT [N.Y. St. Finance Law §187 *et seq.*];
CHICAGO FALSE CLAIMS ORDINANCE [Municipal
Code of Chicago §1-22-010-§1-22-060]; NEW JERSEY
FALSE CLAIMS ACT [N.J. STAT. § 2A:32C-1-17];
RHODE ISLAND FALSE CLAIMS ACT R.I. GEN.
LAWS §9-1.1-1 -9.11-1.8; OKLAHOMA MEDICAID
FALSE CLAIMS ACT 63 OKL. ST. §5053-5053.7;
WISCONSIN STATUTE § 20.931 FOR FALSE CLAIMS
FOR MEDICAL ASSISTANCE; NORTH CAROLINA
FALSE CLAIMS ACT N.C. Gen. Stat. § 1-605-618,
§108A-63; MINNESOTA FALSE CLAIMS ACT [Minn.
Stat. §15C.01 *et seq.*]; .]; the COLORADO MEDICAID
FALSE CLAIMS ACT, C.R.S. §25.5-4-304, *et seq.*; the
CONNECTICUT FALSE CLAIMS ACT, CHAPTER 319v
Sec. 17b-301a *et seq.*; and the MARYLAND FALSE
HEALTH CLAIMS ACT OF 2010, Subtitle 6, False
Claims Against State Health Plans and State Health
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NINTH AMENDED COMPLAINT

Plaintiff-Relator Allison Zayas (“Plaintiff-Relator”), through her undersigned attorneys, on behalf of the United States of America (“United States”), and the State of California, the State of Delaware, the State of Florida, the State of Georgia, the State of Illinois, the State of Hawaii, the State of Indiana, the State of Louisiana, the Commonwealth of Massachusetts, the State of Michigan, the State of New Mexico, the State of Montana, the State of New Hampshire, the State of New York, the State of Nevada, the State of Tennessee, the Commonwealth of Virginia, the State of New Jersey, the State of Rhode Island, the State of Oklahoma, the State of Wisconsin, the State of North Carolina, the State of Minnesota, the State of Connecticut, the State of Colorado, the State of Maryland, the State of Washington, the City of Chicago, and the District of Columbia (collectively, “the States and City”), for her Ninth Amended Complaint against AstraZeneca LP, AstraZeneca Pharmaceuticals LP, AstraZeneca, LP, and AstraZeneca Pharmaceuticals, LP (collectively “Defendant”) alleges as follows:

I. INTRODUCTION

1. This is an action, by and through Plaintiff-Relator Allison Zayas, to recover treble damages and civil penalties on behalf of the United States, the States, and City of Chicago arising from false and/or fraudulent records, statements and claims made, used and/or caused to be made, used or presented by Defendant AstraZeneca and/or its agents, and employees in violation of the federal False Claims Act, 31 U.S.C. § 3729 *et seq.*, and the state and City laws referred to in paragraph 2 of this Complaint.

2. Defendant AstraZeneca's acts also constitute violations of the California False Claims Act, Cal. Gov. Code §12650 *et seq.*; the Delaware False Claims & Reporting Act, 6 Del. C. §1201 *et seq.*; the District of Columbia Procurement Reform Amendment Act, D.C. Code Ann. §1-1188.14 *et seq.*; the Florida False Claims Act, Fla. Stat. Ann. § 68.081 *et seq.*; the Georgia State False Medicaid Claims Act, Ga. Code 49-4-168 *et seq.*; the Illinois Whistle Blower Reward & Protection Act ,740 ILCS § 175 *et seq.*; the Hawaii False Claims Act, Haw. Rev. Stat. § 661-21 (a)(3); the State of Indiana False Claims And Whistleblowers Protection Act, Ind. Code Ann. § 5-11-5.5-1-5-11-5.5-18; the Louisiana False Claims Act, La. Rev. Stat. Ann. § 46:439.1 *et seq.*; the Massachusetts False Claims Law, Mass. Gen. Laws ch. 12 § 5 *et seq.*; the State of Michigan Medicaid False Claims Act, Mich. Comp Laws § 400.603,606 and 607; the State of Montana False Claims Act, Mont. Code Ann. § 17-8-403,17-8-410; the State of New Mexico Medicaid False Claims Act, N.M. Stat. Ann. § 27-14-1-27-14-15; the New Hampshire False Claims Act, New Hamp. Stat. 167:61-b; the New York False Claims Act, N.Y. St. Finance Law § 187 *et seq.*; the Nevada False Claims Act, Nev. Rev. Stat. Ann. § 357.010 *et seq.*; the Tennessee Medicaid False Claims Act, Tenn. Code Ann. §71-5-181 *et seq.*; the City of Chicago False Claims Ordinance, Municipal Code of Chicago §1-22-010-§1-22-060; the New Jersey False Claims Act, N.J. STAT. §2A:32C-1-17; the State of Rhode Island False Claims Act, R.I. Gen. Laws § 9-1.1-1

– 9-1.1-8; the State of Wisconsin Statute, Wis. Stat. § 20.931 for False Claims for Medical Assistance; the State of Oklahoma Medicaid False Claims Act 63 Okl. St. §5053; the North Carolina False Claims Act N.C. Gen. Stat. § 1-605-618, §108A-63; the Minnesota False Claims Act, Minn. Stat. § 15.C01 *et seq.*; and the Virginia Fraud Against Taxpayers Act, Va. Stat. Ch. 842, Art. 19.1, §8.01-216.1 *et seq.*; the Colorado Medicaid False Claims Act, C.R.S. §25.5-4-304, *et seq.*; the Connecticut False Claims Act CHAPTER 319v Sec. 17b-301a *et seq.*; and the Maryland False Health Claims Act of 2010, Subtitle 6, False Claims Against State Health Plans and State Health Programs, §2-601 *et seq.*; and the State of Washington Medicaid Fraud False Claims Act (collectively, the “State and City False Claims Acts”).

3. This matter involves illegal marketing practices by Defendants AstraZeneca LP, AstraZeneca Pharmaceuticals LP, AstraZeneca, LP, and AstraZeneca Pharmaceuticals, LP (jointly “AstraZeneca” or “AZ”).

4. Since at least 1997, Defendant AstraZeneca has been engaged in an illegal marketing scheme for, among other things, the purpose of increasing the sale of its drugs Seroquel[®] (“Seroquel”) and Seroquel XR[®] (“Seroquel XR”). The generic name for Seroquel and Seroquel XR is quetiapine.

5. Plaintiff-Relator Allison Zayas was a specialty sales representative for AstraZeneca in its psychiatry sales force. Among other things, she was responsible for the sale of Seroquel XR in Staten Island, New York and parts of Brooklyn, New York. She has also been responsible for the promotion of Seroquel in these areas. Because of her position, she has unique knowledge of the sales and marketing efforts behind both Seroquel and Seroquel XR. Furthermore, because of her position, she has unique knowledge of how AstraZeneca deliberately misrepresented the

safety profile of Seroquel and Seroquel XR and promoted Seroquel and Seroquel for off-label purposes.

6. Relator has served a copy of each prior Complaint and requisite disclosure statements on the federal government and every State and City that is a party to the Complaint. The disclosure statements were and are supported by material evidence.

7. Relator has complied with all service requirements for the federal government and every State and City that is a party to the Complaint.

8. Relator will serve a copy of this Complaint on the federal government and every State and City that is a party to the Complaint.

9. As required by the state, federal and city False Claims Acts and ordinances, this Complaint is being filed under seal and shall not be served on the Defendant until the court so orders.

10. The allegations contained herein are not based upon any public disclosure.

11. Unless otherwise stated herein, Ms. Zayas is the original source of the information upon which this complaint is based.

12. Unless otherwise stated herein, Ms. Zayas has direct and independent knowledge on which the allegations herein are based and has voluntarily provided this information to the United States, the various states and the City of Chicago before filing this action.

II. PARTIES

13. The United States of America, the States and City of Chicago, are the plaintiffs for whom recovery is sought for false and fraudulent claims submitted to Medicaid and other government-funded health programs, including Champus/TriCare and Veteran's Administration funded programs, as well as those of the respective States and City plaintiffs.

14. Plaintiff-Relator Allison Zayas is a citizen and resident of the State of New York. She brings this action on her own behalf and on behalf of the United States pursuant to 31 U.S.C. § 3730(b)(1) and the respective States and City whistleblower statutes cited in paragraph 2 of this Complaint.

15. Plaintiff-Relator worked for AstraZeneca or an AstraZeneca sales contractor force for more than four years.

16. Defendants AstraZeneca Biopharmaceuticals, Inc., AstraZeneca Pharmaceuticals, LP and AstraZeneca, LP are Delaware corporations with their principal place of business at 1800 Concord Pike, Wilmington, Delaware. AstraZeneca is primarily engaged in the manufacture and sale of pharmaceuticals.

17. Defendant AstraZeneca PLC is a public limited company incorporated under the laws of England and Wales with its principal place of business at 15 Stanhope Gate, London, England, United Kingdom.

18. Defendants AstraZeneca LP, AstraZeneca Pharmaceuticals LP, AstraZeneca, LP, AstraZeneca Pharmaceuticals, LP, and AstraZeneca PLC are referred to collectively herein as “Defendant”, “AstraZeneca” or “AZ”.

19. AstraZeneca sells its pharmaceutical products throughout the United States, including in the Eastern District of New York.

20. Defendant has been the subject of numerous government investigations related to its illegal marketing and pricing practices.

21. On June 20, 2003 AstraZeneca pleaded guilty to a healthcare crime and agreed to pay \$355 million to resolve criminal charges and civil liabilities in connection with its drug pricing

and marketing practices with regard to Zoladex, a drug sold by AstraZeneca and used primarily for the treatment of prostate cancer.

22. As part of the Zoladex Settlement, AstraZeneca entered into a Corporate Integrity Agreement (“CIA”) with the federal government.

23. In order to comply with this CIA, AstraZeneca had to issue a “Code of Conduct” for all of its employees.

24. The April 2008 “Code of Conduct” stated in relevant part:

AstraZeneca’s policy is to disclose information in a timely manner, as necessary, to comply with all relevant legal and regulatory requirements. All such disclosures must be accurate and not misleading, with no material* omissions. This policy applies to all information, whether favourable or unfavourable to AstraZeneca.

25. Despite this statement, as will be addressed *infra*, AstraZeneca has made a number of material inaccurate and misleading statements about Seroquel’s effect on the QT/QTc interval to the Food and Drug Administration (“FDA”), physicians, State Drug Utilization Boards and State Pharmacy and Therapeutics Boards.

26. As will be addressed *infra*, AstraZeneca misrepresented material information about Seroquel’s effect on the QT/QTc interval to the FDA since at least January 2003.

27. As will be addressed *infra*, AstraZeneca withheld material information about Seroquel’s effect on the QT/QTc interval and AstraZeneca’s decisions about the warnings related to QT/QTc prolongation to both the April 8, 2009 FDA Advisory Committee and the June 8-9,

2009 FDA Advisory Committee that were held concerning Seroquel XR and Seroquel respectively.

28. As will be discussed *infra*, AstraZeneca withheld material information about Seroquel's effect on the QT/QTc interval to the FDA in 2010.

29. In April 2010, AstraZeneca agreed to pay \$524 million to resolve allegations that AstraZeneca illegally marketed Seroquel from January 1, 2001 through December 31, 2006.

30. On April 27, 2010 AstraZeneca entered into a Corporate Integrity Agreement ("CIA") with the federal government. As will be explained *infra*, AstraZeneca violated the terms of this CIA with respect to its promotion of Seroquel and Seroquel XR and the false statements it made to the FDA concerning Seroquel and Seroquel XR's effect on the QT/QTc interval.

31. On July 29, 2010 AstraZeneca received an "Untitled Letter" from the FDA regarding its promotional efforts behind Seroquel XR. The letter reads in relevant part:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed AstraZeneca LP's (AZ) MDD (major depressive disorder) leave behind sheet 1 2010 (281061) (leave behind sheet) for its drug product, SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets (Seroquel XR). The leave behind sheet is misleading because it overstates the efficacy of Seroquel XR and omits material facts and risks associated with the drug. Thus, the leave behind sheet misbrands Seroquel XR in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). Cf. 21 CFR 202.1(e)(6)(i) & (e)(7)(i).

III. FACTUAL ALLEGATIONS

A. General Information Related to Seroquel and Seroquel XR

32. Seroquel and Seroquel XR are classified as both atypical antipsychotics and neuroleptics. The active ingredient for both agents is quetiapine.

33. Seroquel is the immediate release version of quetiapine whereas Seroquel XR is the extended release version of the drug.

34. AstraZeneca submitted separate new drug applications for both Seroquel and Seroquel XR.

35. On December 4, 2009, the FDA approved Seroquel for the treatment of schizophrenia in children ages 13 through 17 and for the acute treatment of manic episodes with bipolar 1 disorder in children ages 10 through 17. Prior to this date, Seroquel was not approved for use in children or adolescents.

36. However, prior to this date the 2010 edition of the American Society of Health-System Professionals Drug Information (“ASHS Compendia”) stated that quetiapine’s “[s]afety and efficacy [is] not established in children younger than 18 years of age.”

37. Seroquel has the following indications:

- Schizophrenia in adults
- Schizophrenia in children ages 13 through 17
- Acute treatment of manic episodes with bipolar 1 disorder in children ages 10 through 17
- Treatment of manic episodes associated with bipolar 1 disorder in adults, both as monotherapy and as an adjunct to lithium or divalproex
- Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex in adults

38. Seroquel XR has the following indications:

- Maintenance treatment of schizophrenia in adults
- Treatment of bipolar depression and bipolar mania in adults
- Adjunctive treatment for major depressive disorder in adults

39. Consequently, Seroquel XR is not indicated for the treatment of children or adolescents. Seroquel received its limited pediatric indications in December 2009.

40. Seroquel XR has been an extremely successful drug for AZ. Sales of Seroquel XR in the United States accounted for 3.4% of Seroquel sales in 2008, or \$102.5 million.

41. In 2009, sales of Seroquel XR in the United States accounted for 11.1% of Seroquel sales, or \$379 million.

42. From 2008 to 2009, prescriptions for Seroquel XR increased 195%. First quarter 2010 sales of Seroquel in the United States, which include Seroquel XR, were \$913 million, indicating a growth of 14% from first quarter 2009.

43. Since its launch, sales of Seroquel XR have totaled over \$481 million in the United States. If 2010 first quarter sales are included, total sales of Seroquel XR should total well over \$600 million.

44. The combined United States sales of Seroquel and Seroquel XR in 2009 totaled \$3.416 billion.

B. AstraZeneca's April 2010 Corporate Integrity Agreement

45. Within 120 days of entering into the CIA with the federal government, AstraZeneca had to implement new "Policies and Procedures" to address the way it sold and marketed its drugs in the United States.

46. The CIA called for the development of new "Policies and Procedures" related to whom AstraZeneca would sample its drugs, how it would incentivize its sales force and how it would compile "call plans" for its sales force.

47. Portions of the CIA read in relevant part:

- i. the development, implementation, and review of call plans for sales representatives who promote Government Reimbursed Products. For each Government Reimbursed Product, the Policies and Procedures shall require that AstraZeneca review the call plans for the product and the bases upon, and circumstances under which HCPs and HCIs belonging to specified medical specialties or types of clinical practice are included in, or excluded from, the call plans. The Policies and Procedures shall also require that AstraZeneca modify the call plans as necessary to ensure that AstraZeneca is promoting Government Reimbursed Products in a manner that complies with all applicable Federal health care program and FDA requirements. The call plan reviews shall occur at least annually and shall also occur each time when the FDA approves a new or additional indication for a Government Reimbursed Product;

- q. compensation (including through salaries, bonuses, and contests) for Relevant Covered Persons who are sales representatives. These Policies and Procedures shall: 1) be designed to ensure that financial incentives do not inappropriately motivate such individuals to engage in improper promotion, sales, and marketing of AstraZeneca's Government Reimbursed Products; and 2) include mechanisms, where appropriate, to exclude from incentive compensation sales that may indicate off-label promotion of Government Reimbursed Products;

48. To date, AstraZeneca has only taken partial steps to comply with the CIA.

49. On May 17, 2010, the psychiatry sales force received an email from Central Nervous System Business Alignment Manager Stephanie Bauder concerning the removal of neurologists from representatives' call plans. The email reads in relevant part:

CNS Leaders,

This email contains a very important update and action required for this CSTP¹ session with supporting information. Please cascade this information to your teams.

IMPORTANT UPDATE/ACTION REQUIRED:

Based on the feedback you provided during Period 1, the brand team has approved the removal of ALL Neurologists from your call plan.

ACTION REQUIRED: Please remove ALL Neurologists from your call plan with a reason code 'Reassign to Other Selling Team'. The removal of these prescribers removes workload that will need to offset in order to satisfy the business rules (and thus check back in your STP). As a result, please add additional calls to your STP through adding frequency to your key and high decile physicians. DSMs – please review this change during the DSM review period.

50. This email definitively establishes that the sales force itself was concerned about the propriety of promoting Seroquel and Seroquel XR to neurologists because, by definition, neurologists can only prescribe Seroquel XR for off-label purposes because they do not treat any of the conditions that either Seroquel or Seroquel XR is indicated to treat.

51. Plaintiff-Relator took a "quiz" meant to test her knowledge of the terms of the Corporate Integrity Agreement.

¹ CSTP – Customer Strategic Targeting Plan.

52. One of the questions in the “quiz” asked her the following: “What is the major purpose of sampling?” The answer to the question was: **“To help the healthcare provider and patient to evaluate the product in actual practice.”**

53. Accordingly, AstraZeneca directed its sales force to distribute samples for use in “actual practice” and with no regard to whether the resulting prescription would be for inherently dangerous and/or off-label purposes.

54. AstraZeneca was very successful in both its sampling and detailing efforts to neurologists for Seroquel XR. Below please find a selection of neurologists from New York and New Jersey with their name, address, the number of sales representative calls made on them, the number of samples they received and the “new” Seroquel XR prescriptions these physicians wrote from January 2008 through August 2009:

Name	Address	Sales rep calls	Samples	New SQL XR scripts
Dr. Yanchun Zhang	111 East Northfield Rd., Livingston, NJ	14	129	133
Dr. J. Camacho-Pantoja	471 Barnum Ave., Bridgeport, CT	42	352	75
Dr. Mala Iyer	2780 Middle Country Rd Ste 306, Lake Grove, NY	21	476	66
Dr. Eugenio Tassy	4277 Hempstead Tpke, Ste 104, Bethpage, NY	23	138	46

55. Thus, from January 2008 through August 2009 Drs. Zhand, Camacho-Pantoja, Iyer and Tassy collectively were called on by AZ representatives 100 times, received 1095 Seroquel XR samples, and wrote 320 “New” off-label prescriptions including prescriptions paid for by

State Medicaid agencies. These “New” prescriptions do not account for subsequent refills of these prescriptions.

56. Although Ms. Bauder states that the changes to the call plan related to neurologists were a result of the “feedback” from the sales force, in fact the changes were required if AstraZeneca were to abide by the conditions of the Corporate Integrity Agreement.

57. Importantly, child psychiatrists still remain on the representatives’ call plans. Thus, representatives **still provide child psychiatrists with samples and are directly incentivized to sell Seroquel XR to child psychiatrists for use in children even though Seroquel XR has no indication for use in children.** Thus, by definition, child psychiatrists can only prescribe Seroquel XR for off-label purposes.

58. Nevertheless, AstraZeneca was very successful in both its sampling and detailing efforts to child psychiatrists for Seroquel XR. Below please find a selection of child psychiatrists from New York, New Jersey, and Connecticut with their name, address, the number of sales representative calls made on them, the number of samples they received and the “new” Seroquel XR prescriptions these physicians wrote from January 2008 through August 2009:

Name	Address	Sales rep calls	Samples	New SQL XR Scripts
Dr. Lazaro Pomeraniec	2819 Main Street, Bridgeport, CT	50	1,687	87
Dr. Claudio Dicoskiy	681 Broadway, Patterson, NJ	29	827	53
Dr. Carol Dobrzynski	2890 Yorktowne Blvd., Brick, NJ	44	725	64
Dr. Matthew Pitera	222 Oak Ave., Ste 2, Toms River, NJ	33	668	49
Dr. Barbara Winograd	280 Amboy Ave., Ste 2, Metuchen, NJ	29	550	48

59. Thus, from January 2008 through August 2009, Drs. Pomeranec, Dicovski, Dobryzynski, Pitera, and Winograd were collectively called on by AZ representatives 185 times, received 4457 Seroquel XR samples and wrote 301 “New” off-label prescriptions including prescriptions paid for by State Medicaid agencies. These “New” prescriptions do not account for subsequent refills of these prescriptions.

60. Ms. Bauder’s email also includes a section that helps representatives identify which physicians “are not appropriate for promotion.” This section reads in relevant part:

Touchstone updated to identify HCPs who are not appropriate for promotion

Recently there have been questions from the field about samples being rejected for HCPs who previously have been sampled successfully. Sales and Brand Leadership along with Compliance have worked together to continue to ensure that we are detailing and sampling only those HCPs who are appropriate for promotion of our products. HCPs who are not appropriate for promotion of specific products are not eligible to receive samples and should not be detailed on for those products. This includes specified HCPs who have been designated as “blocked” from promotion for a specific product or who are part of a specialty that has been “excluded” from promotion of a specific product.

“Blocked” HCPs are not to be promoted to regardless of their specialty designation. Blocks can be at a brand level or a corporate level.

“Excluded” HCPs are excluded from promotion based on their specialty designation. Exclusions are done on a brand-by-brand basis and are related to the brand’s label and FDA approved indications.

Per AstraZeneca policy, you may not detail or sample HCPs for products for which they have been excluded or blocked. If you sample an HCP who has been excluded or blocked for a product, the sample request will be rejected with a reason code indicating, “Specialist (HCP) Not Eligible for requested samples”.

61. Ms. Bauder’s email is important for several reasons. First, it identifies a body of physicians who previously were “sampled successfully” but are now, because of the CIA, “no longer eligible” to receive samples. Secondly, it effectively concedes that it was inappropriate for these groups of physicians to be called on by sales representatives. Lastly, it is a remedial measure that comes over two years late and after millions of dollars worth of off-label XR prescriptions have been paid for by the government.

C. Medicaid and Medicare Part D Drug Utilization Review Requirements

62. All federal government prescription programs require that a prospective drug utilization review (“DUR”) be performed **before** the prescription is filled. The DUR process includes a drug-drug interaction screen. The DUR is performed to ensure the beneficiary is not

harmful by the drug and, by definition, to ensure that taking the drugs together is medically necessary given the risks inherent in taking the drugs together.

63. Prospective drug utilization review is also known as concurrent drug utilization review.

64. Because drug manufacturers have the most information related to the hazards of ingesting their drugs, the prospective drug utilization review program is predicated on drug manufacturers following federal law and amending the labels of their drugs to include a warning (including those related to fatal drug interactions) as soon as there is reasonable evidence of a serious hazard with a drug; a causal relationship need not have been proved.

65. In October 2003, the Inspector General of the Department of Health and Human Services published “State Strategies to Contain Medicaid Drug Costs” (“the 2003 OIG Medicaid Cost Containment Report”).

66. In this document, the Inspector General stated that prospective drug utilization reviews are important for “**drug cost containment** because they help prevent duplicative, **contraindicated**, or medically unnecessary prescriptions **from being dispensed**.” (emphasis added).

67. 42 U.S.C. §1396r-8(g)(1)(A)(i-iii) requires that states provide a drug review program in order to assure that Medicaid prescriptions are appropriate, medically necessary and:

“are not likely to result in **adverse medical results**. The program shall be designed to educate physicians and **pharmacists** to identify and reduce the frequency of patterns of fraud, abuse, gross overuse, or **inappropriate or medically unnecessary care**, among physicians, **pharmacists**, and patients, or associated with specific drugs or groups of drugs, as well as **potential and actual severe adverse reactions** to drugs including education on therapeutic appropriateness, overutilization and underutilization, appropriate use of generic products, therapeutic duplication, drug-disease contraindications, **drug-drug interactions**, incorrect drug dosage or duration of drug treatment, drug-allergy interactions, and **clinical abuse/misuse**. (emphasis added).

68. 42 U.S.C. §1396r-8(g)(2)(A)(i) provides:

2) Description of program

Each drug use review program shall meet the following requirements for covered outpatient drugs:

(A) Prospective drug review

(i) The State plan shall provide for a review of drug therapy **before each prescription is filled or delivered to an individual receiving benefits under this subchapter**, typically at the point-of-sale or point of distribution. The review shall include screening for potential drug therapy problems due to therapeutic duplication, drug-disease contraindications, **drug-drug interactions (including serious interactions with nonprescription or over-the-counter drugs)**, incorrect drug dosage or duration of drug treatment, drug-allergy interactions, and clinical abuse/misuse. Each State shall use the **compendia** and literature referred to in paragraph (1)(B) as its source of standards for such review. (emphasis added).

69. The “compendia” are used and relied upon by the States to inform “standards” for review of drug-drug interactions.

70. Upon review of the compendia and reliance upon the Seroquel prescribing information, State Medicaid Drug Utilization Review Boards now classify the use of Seroquel with other QTc prolonging medications as “contraindicated.”

71. Each State has set up a Drug Utilization Review Board to help ensure the safety of Medicaid beneficiaries receiving pharmaceuticals.

72. In New York, Social Services Law § 369 AA-8 defines the “Compendia” as follows:

8. “Compendia” shall mean those resources widely accepted by the medical profession in the efficacious use of drugs which is based on, but not limited to, these sources: “American Hospital Formulary Services Drug Information,” “U.S. Pharmacopeia - Drug Information,” “AMA Drug Evaluations,” the peer-reviewed medical literature, and **information provided from the manufacturers of drug products**. (emphasis added).

73. In Texas, the Compendia is comprised of a number of different sources that include “[m]anufacturer websites and package inserts.”

74. Each State Drug Utilization Review Board materially relies upon information provided to it to inform its drug-drug interaction screening process.

75. 42 C.F.R. § 423.153(c)(4) requires that Medicare Part D sponsors have internal medication error and reduction measures and systems that address ways to reduce medication errors and adverse drug interactions, and improve medication use.

76. 42 C.F.R. § 423.153(c)(5) requires that Part D sponsors provide CMS with information concerning the plan’s quality assurance measures and systems to reduce medication errors and adverse drug interactions, and improve medication use.

77. All states allow a pharmacist to refuse to fill a prescription if, in his/her judgment, filling the prescription would compromise the safety of the patient.

78. For example, in New York NYS § 63.6 (b)(8)(ii)(d)(5) provides:

5. Nothing in this subparagraph shall prevent a pharmacist or pharmacy intern from refusing to dispense a prescription if, in his or her professional judgment, potential adverse effects, interactions or other therapeutic complications could endanger the health of the patient.

79. For example, in Pennsylvania 6 Pa. Code § 27.18 (c) provides:

(c) A pharmacist may decline to fill or refill a prescription if the pharmacist knows or has reason to know that it is false, fraudulent or unlawful, or that it is tendered by a patient served by a public or private third-party payor who will not reimburse the pharmacist for that prescription. A pharmacist may not knowingly fill or refill a prescription for a controlled substance or nonproprietary drug or device if the pharmacist knows or has reason to know it is for use by a person other than the one for whom the prescription was written, or will be otherwise diverted, abused or misused. In addition, **a pharmacist may decline to fill or refill a prescription if, in the pharmacist’s professional judgment exercised in the interest of the safety of the patient, the pharmacist believes the prescription should not be filled or refilled. The pharmacist shall explain the decision to the patient. If necessary the pharmacist shall attempt to discuss the decision with the prescriber.** (emphasis added).

80. For example, in New Jersey Section 45:14-66 of the New Jersey Pharmacy Act provides:

27. a. A pharmacist shall conduct a drug utilization review before each new medication is dispensed or delivered to a patient.

b. A pharmacist shall conduct a prospective drug utilization review in accordance with the provisions of this section before refilling a prescription or medication order to the extent he deems appropriate in his professional judgment.

c. A pharmacist shall exercise independent professional judgment as to whether or not to dispense or refill a prescription or medication order. In determining to dispense or refill a prescription or medication order, the decision of the pharmacist shall not be arbitrary but shall be based on professional experience, knowledge or available reference materials. (emphasis added).

81. For example, in Kansas KSA 65-1642 provides:

KSA 65-1642- Upon receipt of a prescription, the pharmacist shall examine the patients medication profile record before dispensing the medication to determine the possibility of harmful drug interaction or reaction to medication. Upon recognizing the a potential harmful drug interaction or reaction to medication, the pharmacist shall take appropriate action to avoid or minimize the problem which shall, if necessary include consultation with the prescriber with documentation of actions taken on the prescription record. (emphasis added).

82. For example, Texas law allows pharmacists to refuse to fill prescriptions if, in the opinion of the pharmacist, filling the prescription will compromise the patient's health. The Texas State Board of Pharmacy provides the following patient information:

Is the pharmacist required to fill my prescription?

Occasionally, pharmacists may refuse to fill a prescription if they believe that filling the prescription is not in the best interest of your health. Some of the reasons a pharmacist may refuse to fill a prescription include:

- the pharmacist is concerned that the medication will interact badly with another drug you are taking; (emphasis added).

83. For example, California law allows a pharmacist to refuse to fill a prescription if the pharmacist “determines that the prescribed drug or device would cause a harmful drug interaction or would otherwise adversely affect the patient’s medical condition.” The California law reads in relevant part:

733. Dispensing Prescription Drugs and Devices

(a) No licentiate shall obstruct a patient in obtaining a prescription drug or device that has been legally prescribed or ordered for that patient. A violation of this section constitutes unprofessional conduct by the licentiate and shall subject the licentiate to disciplinary or administrative action by his or her licensing agency.

(b) Notwithstanding any other provision of law, a licentiate shall dispense drugs and devices, as described in subdivision (a) of Section 4024, pursuant to a lawful order or prescription unless one of the following circumstances exists:

(1) Based solely on the licentiate's professional training and judgment, dispensing pursuant to the order or the prescription is contrary to law, or the licentiate determines that the prescribed drug or device would cause a harmful drug interaction or would otherwise adversely affect the patient's medical condition.

84. For example, Illinois law provides:

e) Pharmacies have a duty to deliver lawfully prescribed drugs to patients and to distribute nonprescription drugs approved by the U.S. Food and Drug Administration for restricted distribution by pharmacies, or to substitute a generic drug as permitted in Section 25 of the Act in a timely manner, or to contact the prescriber to obtain authorization to dispense a different drug that produces a similar clinical effect in a timely manner, except for the following or substantially similar circumstances:

1) When, in the pharmacist's professional judgment, after screening for potential drug therapy problems due to therapeutic duplication, drug-disease contraindications, drug-drug interactions (including, but not limited to, serious interactions with nonprescription or over-the-counter drugs), drug-food interactions, incorrect drug dosage or duration of drug treatment, drug-allergy interactions, or clinical abuse or misuse, pursuant to subsection 3(aa) of the Act, she or he determines that the drug should not be dispensed due to one of the foregoing clinical reasons:

85. For example, Florida law provides that “the pharmacist shall, **prior to the actual physical transfer, interpret and assess the prescription** order for potential adverse reactions, **interactions**, and dosage regimen she or he deems **appropriate in the exercise of her or his**

professional judgment, and the pharmacist shall certify that the medicinal drug called for by the prescription **is ready for transfer.**" (emphasis added).

86. For example, Alabama law provides:

680-X-2.22. CODE OF PROFESSIONAL CONDUCT.

(1) Pharmacists and pharmacies are expected to conduct themselves in a professional manner at all times. The following code provides principles of professional conduct for pharmacists and pharmacies to guide them in their relationship with patients, fellow practitioners, other health professionals and the public.

(2) Violations of any provisions of this rule shall be deemed grounds for disciplinary action whenever the Board shall find a preponderance of evidence to such violations.

(a) A pharmacist and a pharmacy should hold the health and safety of patients to be of first consideration and should render to each patient the full measure of professional ability as an essential health practitioner.

(b) A pharmacist and a pharmacy should never knowingly condone the dispensing, promoting, or distributing of drugs or medical devices, or assist therein, that are not of good quality, that do not meet standards required by law, or that lack therapeutic value for the patient.

87. In order to ensure the safety of Medicaid beneficiaries, pharmacists are paid a drug dispensing fee (that encompasses reimbursement for prospective drug utilization review) by state Medicaid programs that can be up to 43% greater than private insurance plans' reimbursement rates for these same services.

88. On May 21, 2004 the Centers for Medicare & Medicaid Services published update guidelines on what constituted "Immediate Jeopardy" for patients receiving Medicare and Medicaid services.

89. The guidelines applied to the following entities that provide services for Medicaid and Medicare beneficiaries:

These guidelines apply to all certified Medicare/Medicaid entities (excluding CLIA) and to all types of surveys and investigations: certifications, recertifications, revisits, and complaint investigations. In these guidelines, "entity" applies to all Medicare/Medicaid certified providers, suppliers, and facilities. "Surveyor" represents both surveyors and complaint investigators. "Team" represents either a single surveyor or multiple surveyors. The term "Immediate Jeopardy" replaces the terms "Immediate and Serious Threat" and "Serious and Immediate Threat" for all certified Medicare/Medicaid entities.

90. "Immediate Jeopardy" was defined as follows:

II - Definitions

Immediate Jeopardy - “A situation in which the provider’s noncompliance with one or more requirements of participation has caused, or is likely to cause, serious injury, harm, impairment, or death to a resident.” (See 42 CFR Part 489.3.)

91. The “Immediate Jeopardy Triggers” were listed and included the following:

Triggers	
Issue	Triggers
D Failure to protect from undue adverse medication consequences and/or failure to provide medications as prescribed.	<ol style="list-style-type: none"> 1. Administration of medication to an individual with a known history of allergic reaction to that medication; 2. Lack of monitoring and identification of potential serious drug interaction, side effects, and adverse reactions; 3. Administration of contraindicated medications; 4. Pattern of repeated medication errors without intervention; 5. Lack of diabetic monitoring resulting or likely to result in serious hypoglycemic or hyperglycemic reaction; or 6. Lack of timely and appropriate monitoring required for drug titration.

92. From 1997 through January 2010, there was no warning about the dangers caused by the concomitant use of Seroquel with QT/QTc prolonging agents in the United States Seroquel or Seroquel XR labels.

93. There were, however, warnings about such dangers in the Seroquel labels in the European Union, the United Kingdom, and Australia prior to that date.

94. As will be addressed *infra*, since at least December 2000, one of AstraZeneca’s “Key Success Factors” for its Seroquel franchise was “defending” the Seroquel label from “FDA label threats” related to QT/QTc prolongation.

95. From January 2010 until June 2011, the Seroquel label only advised “caution” when Seroquel was used with drugs known to cause increases in the QT/QTc interval.

96. In June 2011, the FDA directed that the label advise that the use of Seroquel with drugs known to cause QT/QTc prolongation like methadone should be “**avoided**.”

97. State Drug Utilization Review Boards rely on pharmaceutical manufacturers to comply with federal law and amend their labels as soon as there is “reasonable association of a serious hazard with a drug.” There was a “reasonable association of a serious hazard” of taking quetiapine with other drugs known to cause increases in the QT/QTc interval since at least 1997.

98. State Drug Utilization Boards relied on quetiapine’s prescribing information to determine whether or not quetiapine causes prolongation of the QT/QTc interval.

99. State Drug Utilization Boards relied on the quetiapine’s prescribing information to determine whether or not it was safe for quetiapine to be used concomitantly with other drugs known to increase the QT/QTc interval.

100. AstraZeneca Medical Affairs representatives have made numerous direct presentations to every State’s Drug Utilization Review Board concerning quetiapine.

101. While doing so, the representatives have referred **specifically** to quetiapine’s prescribing information.

102. For example, on October 20, 2011, AstraZeneca Medical Affairs representative Parshotam Sachdeva provided a “testimonial” to the New York State Drug Utilization Review Board. His prepared remarks made numerous references to the Seroquel and Seroquel XR prescribing inserts (“prescribing information”) including:

BOXED WARNING

- The prescribing information for SEROQUEL XR and SEROQUEL contain a boxed warning:
 - Antidepressants increased the risk of suicidal thinking and behavior in short term studies in children, adolescents and young adults with major depressive disorder and other psychiatric disorders.^{2,7}
- SEROQUEL XR is not approved for use in patients less than 18 years of age.²
- Please see the full prescribing information for complete details of boxed warnings, and other warnings and precautions.

REFERENCES:

2. SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets Prescribing Information.

7. SEROQUEL (quetiapine fumarate) Prescribing information

103. At this presentation and others previous AstraZeneca Medical Affairs presentations the New York State Medicaid Drug Utilization Review Board relied on both the Seroquel XR prescribing information and the Seroquel prescribing information to provide information that was not false or misleading so that it could adequately protect New York State Medicaid beneficiaries from actual and potential dangerous drug interactions.

104. The State of Illinois calls its Drug Utilization Review Board the “Illinois Medicaid Drugs & Therapeutic Board.”

105. On March 31, 2011, Amy Hall, Managed Markets Brand Director for Seroquel, sent a letter to the Illinois Bureau of Pharmacy Services and a “similar letter” to “Illinois Medicaid Drug & Therapeutic members” concerning quetiapine. In the letter to the Illinois Bureau of Pharmacy Services, Ms. Hall makes several references to the Prescribing Information for both Seroquel and Seroquel XR and a specific reference to quetiapine’s effect on the QT/QTc interval:

AstraZeneca is committed to responsible promotion of our products, and believes that SEROQUEL and SEROQUEL XR offer proven efficacy across a breadth of indications and are appropriate low-cost branded atypical options that should be part of the Illinois atypical preferred drug list. While we understand that both brands will be available through the prior authorization process, we believe it would be less onerous on physicians if clinical guidelines designed to support the appropriate use of products were implemented rather than a prior authorization applied across physician prescribing. We sent a similar letter to the other Illinois Medicaid Drug & Therapeutics members and request that you collectively consider our comments. Please see the following pages of this letter for Important Safety Information regarding SEROQUEL and SEROQUEL XR. Copies of the complete Prescribing Information for SEROQUEL and SEROQUEL XR have also been included for your reference.

Regards,



Amy Hall
Managed Markets Brand Director – SEROQUEL Franchise

Please see following pages for Important Safety Information and accompanying full Prescribing Information for SEROQUEL and SEROQUEL XR, including Boxed Warnings.

Warnings and Precautions Also Include: the risk of hypothyroidism, hyperprolactinemia, transaminase elevations, priapism, QT prolongation in predisposed patients, and withdrawal.

106. This letter falsely states that QT prolongation is a risk only in “predisposed patients” and omits the January 2010 warning that “caution” should be used when quetiapine is used concomitantly with other drugs known to prolong the QT/QTc interval.

107. Less than three months later in June 2011, FDA directed AstraZeneca to include in the Seroquel labels that the use of quetiapine “**should be avoided**” with other drugs known to increase the QT/QTc interval.

108. Both in this correspondence and in preceding correspondence Illinois Medicaid Drug and Therapeutic Board relied on both the Seroquel XR prescribing information and the Seroquel prescribing information to provide information that was not false or misleading so that it could adequately protect Illinois State Medicaid beneficiaries.

109. States are required to submit on an annual basis a “retrospective drug use review” of Medicaid beneficiary claims data and other records in order to identify patterns of fraud, abuse, gross overuse, or **inappropriate** or medically unnecessary care, among physicians, pharmacists and individuals receiving benefits. 42 U.S.C. §1396r-8(g)(2)(B) reads in its entirety:

B) Retrospective drug use review

The program shall provide, through its mechanized drug claims processing and information retrieval systems (approved by the Secretary under section 1396b (r) of this title) or otherwise, for the ongoing periodic examination of claims data and other records in order to identify patterns of fraud, abuse, gross overuse, or **inappropriate or medically unnecessary care**, among physicians, pharmacists and individuals receiving benefits under this subchapter, or associated with specific drugs or groups of drugs. (emphasis added).

D. Safety information related to Seroquel and Seroquel XR's effect on the QT/QTc interval of patients taking Seroquel or Seroquel XR with methadone

110. A package insert is a leaflet that, by order of the FDA, must be placed inside the package of every prescription drug. The leaflet must include the trademark for the drug, its generic name, and its mechanism of action; state its indications, contraindications, warnings, precautions, adverse effects, and dosage forms; and include instructions for the recommended dose, time, and route of administration.

111. The package inserts ("prescribing information") for both Seroquel and Seroquel XR indicate that the drugs can cause severe side effects in children, adolescents and adults including weight gain, hyperglycemia, hyperlipidemia, hypertension, hyperprolactinemia, tardive dyskinesia, hypertension, orthostatic hypotension and neuroleptic malignant syndrome.

112. However, there is no information in either Seroquel or Seroquel XR's package inserts related to the danger posed by the concomitant use of either drug with the opiate methadone. Methadone is metabolized by the body's cytochrome P450 enzyme system.

113. Until January 2010, there was no warning about the dangers of using quetiapine with drugs known to prolong the QT/QTc interval like methadone in the United States Seroquel and Seroquel XR labels.

114. European Union regulators have been monitoring methadone/quetiapine drug interactions for at least eight years. Currently, the methadone/quetiapine drug interaction is subject to a European Union Risk Management Plan.

115. On June 16, 2004, the Dutch Medicines Evaluation Board ("MEB") issued its annual safety report for Seroquel which included the following narrative about the quetiapine/methadone drug interaction:

During the current period, 45 reports (16 serious and 29 non-serious) of drug interactions were identified. The possible interactions were seen with:

- Methadone, 4x of which 3 with fatal outcome. This possible interaction would be due to competition for CYP450 3A4 of both compounds.

Assessor's comment: The conclusion of the MAH that the SPC does not need to be changed based on the information about drug interactions is endorsed. However, the above mentioned possible interactions with methadone should be cumulatively reviewed.

The MAH concludes that the SPC does not need to be changed based on the information about drug interactions. This conclusion is endorsed; however the possible interactions with methadone should be cumulatively reviewed.

116. On April 20, 2005, the MEB issued its annual safety report for Seroquel which included the following narrative about the quetiapine/methadone drug interaction:

A cumulative review of possible drug interactions between quetiapine and methadone identified six cases with the events drug interaction (4x), drug toxicity (2x), overdose (1x), hepatic cirrhosis (1x), pulmonary oedema (1x), pulmonary congestion (1x), malaise (1x), lethargy (1x), convulsion (1x), coma (1x) and sedation (1x).

Four of these cases had a fatal outcome. In two of these cases, autopsy reports were available. In one case the drug levels of quetiapine, methadone, sertraline and ethanol were high. In the other case only quetiapine levels were provided.

CYP450 3A4 is the primary metabolic pathway for both quetiapine and methadone. Therefore, quetiapine and methadone would compete for this enzyme and this could result in increased parent drug levels. The events reports have been reported for both quetiapine and/or methadone.

Assessor's comment: Interactions due to competition on CYP450 3A4 has been stated in section 4.5 of the SPC. And concomitant administration of CYP450 3A4 inhibitors is contraindicated.

117. Methadone is metabolized in part by cytochrome P450 3A4 and inhibition of this enzyme will lead to increased and dangerous levels of methadone.

118. Between 1998 and 2003, prescriptions for methadone increased from 500,000 to 1.8 million prescriptions. From 2005 to 2006, unique patient prescriptions for methadone increased 80% with most of this increase largely attributed to pharmacy dispensing rather than self-dispensing methadone maintenance programs ("MMT"). Much of this increase is attributable to physicians prescribing methadone for pain relief.

119. According to a March 2009 Government Accountability Office report, from 1998 to 2005 annual prescriptions of methadone for pain in the United States increased by 700% from 531,000 in 1998 to 4.1 million in 2005.

120. According to a *New York Times* article published July 28, 2010, narcotic pain killers accounted for 7% of all prescribed drugs in 2009 and the number of patients taking long-acting versions of them, including methadone, has increased 30% over the last decade.

121. In March 2009 the Government Accountability Office published a study titled “METHADONE-ASSOCIATED OVERDOSE DEATHS – Factors Contributing to Increased Deaths and Efforts to Prevent Them” that found the following:

The growing availability of methadone through its increased use for pain management is a contributing factor to the rise in methadone-associated overdose deaths. DEA data show that from 2002 to 2007, distribution of methadone to business types associated with pain management—pharmacies and practitioners—almost tripled, rising from about 2.3 millions grams to about 6.5 million grams. In contrast, distribution to OTPs increased more slowly, from about 5.3 million grams to about 6.5 million grams. See table 2 for the numbers for methadone distribution to four business types from 2002 through 2007. Similarly, data from IMS Health, a private company that tracks prescription drug trends, showed that from 1998 through 2006 the number of annual prescriptions of methadone for pain increased by about 700 percent, from about 531,000 in 1998 to about 4.1 million in 2006.

Table 2: Methadone Distribution by Type of Business, 2002 to 2007

	2002	2003	2004	2005	2006	2007
OTPs	5,262,052	5,743,272	6,584,721	6,892,025	7,345,623	6,451,288
Hospitals ^a	309,315	393,685	466,352	521,216	584,144	590,649
Pharmacies	2,329,083	3,274,331	4,246,007	4,863,736	5,986,488	6,442,516
Other practitioners ^b	10,381	15,113	35,492	43,260	51,046	49,503

Source: GAO analysis of DEA methadone distribution data.

122. And, during this time period, there was a concomitant increase in methadone-related deaths. In fact, from 1999 to 2005, poisoning deaths mentioning methadone increased 468%.

123. AZ had constructive knowledge of both the increased utilization of methadone for pain relief and the alarming increase in poisoning deaths mentioning methadone.

124. And, despite this knowledge, AZ directed its sales representatives to call on (“sell”) Seroquel and Seroquel XR to pain physicians and methadone maintenance clinics.

125. AZ had actual knowledge of the potential deadly consequences of concomitant use of quetiapine and methadone as early as 2002, if not sooner.

126. Despite this knowledge, AZ directed, and incentivized, its representatives to sell quetiapine to physicians it knew used quetiapine with methadone including pain and addiction physicians.

127. Methadone is a powerful opiate with a black box warning concerning QTc prolongation.

128. The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. In general, the QT interval represents electrical depolarization and repolarization of the left and right ventricles. A prolonged QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes (“TdP”) and a risk factor for sudden death and cardiac arrest.

129. The relevant section of the black box warning for methadone reads in relevant part:

In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

130. Methadone's prescribing information also contains a warning about the use of methadone with "neuroleptics" like Seroquel and Seroquel XR. The warning reads in relevant part:

Potentially Arrhythmogenic Agents

Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when prescribing methadone concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

131. In November 2006, the FDA issued a Safety Alert ("Alert") about the dangers associated with the use of methadone. The Alert reads in its entirety:

Information for Healthcare Professionals Methadone Hydrochloride text version

FDA ALERT [11/2006]: Death, Narcotic Overdose, and Serious Cardiac Arrhythmias

FDA has reviewed reports of death and life-threatening adverse events such as respiratory depression and cardiac arrhythmias in patients receiving methadone. These adverse events are the possible result of unintentional methadone overdoses, drug interactions, and methadone's **cardiac toxicities (QTc prolongation and Torsades de Pointes)**. Physicians prescribing methadone should be familiar with methadone's toxicities and unique pharmacologic properties. Methadone's elimination half-life (8-59 hours) is longer than its duration of analgesic action (4-8 hours). Methadone doses for pain should be carefully selected and slowly titrated to analgesic effect even in patients who are opioid-tolerant. Physicians should closely monitor patients when converting them from other opioids and changing the methadone dose, and thoroughly instruct patients how to take methadone. Healthcare professionals should tell patients to take no more methadone than has been prescribed without first talking to their physician. (emphasis added).

132. The Alert is significant for several reasons. First, it identifies an injury one would expect when quetiapine is used concomitantly with methadone, namely "cardiac arrhythmias."

133. Secondly, the Alert specifically identifies "drug interactions" as one of the "possible" reasons for the "reports of death and life-threatening adverse events" associated with methadone usage.

134. The Alert provided patients with a specific instruction concerning the specter “drug interactions” pose when using methadone. That instruction reads in its entirety:

“Tell your doctor if you start or stop other medicines **because other medicines can interact with methadone and possibly cause death or life threatening side effects, or result in less pain relief from methadone.**”

135. Lastly, and most significantly, the Alert states that “[p]hysicians prescribing methadone should be familiar with methadone’s toxicities and unique pharmacologic properties.” The warning concerning methadone’s “unique pharmacologic properties” refers to what effect medications like quetiapine have on how the body metabolizes methadone.

136. AstraZeneca had constructive knowledge of this FDA Safety Alert, yet continued to direct sales representatives to call on addiction specialists, methadone maintenance clinics and pain specialists through at least August 2010.

137. In that same month, the FDA also issued a Public Health Advisory titled “Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat.”

138. The Public Health Advisory reads in its entirety:

11/27/2006

FDA has received reports of death and life-threatening side effects in patients taking methadone. These deaths and life-threatening side effects have occurred in patients newly starting methadone for pain control and in patients who have switched to methadone after being treated for pain with other strong narcotic pain relievers. Methadone can cause slow or shallow breathing and **dangerous changes in heart beat that may not be felt by the patient.**

Prescribing methadone is complex. Methadone should only be prescribed for patients with moderate to severe pain when their pain is not improved with other non-narcotic pain relievers. Pain relief from a dose of methadone lasts about 4 to 8 hours. However, methadone stays in the body much longer—from 8 to 59 hours after it is taken. As a result, patients may feel the need for more pain relief before methadone is gone from the body. Methadone may build up in the body to a toxic level if it is taken too often, if the amount taken is too high, or if it is taken with certain other medicines or supplements.

To prevent serious complications from methadone, health care professionals who prescribe methadone should read and carefully follow the methadone (Dolophine) prescribing information.

FDA is issuing this public health advisory to alert patients and their caregivers and health care professionals to the following important safety information:

- Patients should take methadone exactly as prescribed. Taking more methadone than prescribed can cause breathing to slow or stop and can cause death. A patient who does not experience good pain relief with the prescribed dose of methadone, should talk to his or her doctor.
- Patients taking methadone should not start or stop taking other medicines or dietary supplements without talking to their health care provider. Taking other medicines or dietary supplements may cause less pain relief. **They may also cause a toxic buildup of methadone in the body leading to dangerous changes in breathing or heart beat that may cause death.**
- Health care professionals and patients should be aware of the signs of methadone overdose. Signs of methadone overdose include trouble breathing or shallow breathing; extreme tiredness or sleepiness; blurred vision; inability to think, talk or walk normally; and feeling faint, dizzy or confused. If these signs occur, patients should get medical attention right away.

FDA recently approved new prescribing information for methadone products approved for pain control. The information in the new prescribing information is based on a review of the scientific literature completed by FDA. A Medication Guide for patients is planned.

139. Like the FDA Safety Alert, this Public Health Advisory warns that some drugs may cause “a toxic buildup of methadone in the body leading to dangerous changes in breathing or heart beat that may cause death.”

140. Seroquel and Seroquel XR are two of the drugs, which, if used concomitantly with methadone, can cause a toxic buildup of methadone in the body leading to dangerous changes in breathing or heart beat (QTc prolongation) that may cause death. However, the labels for Seroquel and Seroquel XR do not contain any warning about the risk of such a toxic buildup.

141. As will be explained *infra*, AstraZeneca has deliberately obscured, if not hidden, the true dangers posed by the concomitant use of quetiapine and drugs known to increase the

QT/QTc interval, like methadone, to patients, physicians, pharmacists and state Drug Utilization Review Boards.

142. Methadone may interact with central nervous system depressants to produce lethal respiratory depression. In effect, people die from methadone overdose because they simply stop breathing as a result of the depression of the brain's respiratory centers. People taking methadone can also die from cardiac arrhythmias precipitated by the ingestion of methadone with another drug known to increase the QT/QTc interval like quetiapine.

143. Quetiapine also causes respiratory depression but the quetiapine labels do not warn of this dangerous side effect.

144. Quetiapine's widespread use off-label as a sleep agent poses a distinct risk for patients taking methadone. The use of quetiapine with methadone has the synergistic effect of enhancing the respiratory depressive effects and QT/QTc prolonging effects of methadone.

145. In addition, the combination of methadone with other drugs may interfere with other enzymes responsible for methadone's metabolism, thereby increasing methadone's serum concentration and leading to overdose.

146. Pharmacokinetics is the quantitative study of how drugs are taken up, biologically transformed, distributed, metabolized, and eliminated from the body.

147. The labeling for both Seroquel and Seroquel XR contains information concerning the drugs' respective pharmacokinetics.

148. Furthermore, the 2010 edition of ASHS Compendia states that "pharmacokinetic interaction" between quetiapine and other "drugs metabolized by hepatic microsomal enzyme substrates CYP1A2, CYP3A4, CYP2C9, CYP2C19 or CYP2D6" is "unlikely."

149. Methadone label states that methadone is metabolized “principally by cytochrome P-450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent CYP2CP and CYP2D6.” Methadone’s label states in relevant part:

Drug Interactions (see PRECAUTIONS, Drug Interactions)

Methadone undergoes hepatic N-demethylation by cytochrome P-450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone’s effects. Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir–ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with

methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy before making a dosage adjustment.

150. In June 2007, an AstraZeneca funded study titled “Increased (R)-Methadone Plasma Concentrations by Quetiapine in Cytochrome P450s and ABC1 Genotyped Patients” was published in the Journal of Clinical Psychopharmacology (the “Uehlinger study”).

151. Because AstraZeneca funded the Uehlinger study, AZ had access to the results of the study long before June 2007.

152. In fact, the Uehlinger study states in relevant part:

Very recent studies show that methadone can prolong the QT interval and cause torsades de pointes, the use of high methadone doses being a risk factor.^{24,25} Rare cases of QT-interval prolongation have also been shown with quetiapine.²⁶ As the present study was conducted before the cases of torsades de pointes under methadone were published, no electrocardiography was performed, and we can therefore not draw any conclusions regarding this point. This must, however, clearly be examined in future

153. On September 17, 2002, the Archives of Internal Medicine published a study titled, “Torsades de Pointes Associated with Very-High-Dose Methadone.”

154. Accordingly, the Uehlinger study was conducted sometime before September 17, 2002. As the study's sponsor, AstraZeneca had access to the results of the Uehlinger study before September 17, 2002.

155. Consequently, AstraZeneca had knowledge of the results from the Uehlinger study **for almost five years** before the study was published. Additionally, it has been more than eight years since AstraZeneca has had the results of the Uehlinger study. To date, it has not amended the labels for Seroquel and Seroquel XR to include these results.

156. The Uehlinger study measured steady-state plasma concentrations in 14 addict patients in MMT before and after the introduction of quetiapine administered at a mean dosage of 138 mg per day. Neither Seroquel nor Seroquel XR has any FDA approved indications where the quetiapine dose has effect at lower than 150 mg per day.

157. When metabolized in the body, (R)-methadone is the active metabolite for methadone. The increases recorded by the Uehlinger study in (R)-methadone for each patient after initiation of quetiapine were as follows:

Patient 1	8%
Patient 2	<u>85%</u>
Patient 3	3%
Patient 4	<u>42%</u>
Patient 5	<u>60%</u>
Patient 6	20%
Patient 7	<u>-23%</u>
Patient 8	17%
Patient 9	<u>36%</u>

Patient 10	2%
Patient 11	-9%
Patient 12	8%
Patient 13	8%
Patient 14	<u>32%</u>

158. Consequently, the Uehlinger study established that quetiapine can cause anywhere from a 23% decrease to an 85% increase in the active form of methadone.

159. Both data points are clinically significant for different reasons. The patient experiencing nearly a 25% decrease in methadone levels may experience side effects from being under medicated. More disturbingly, the patient experiencing an 85% increase could experience overdose or even death.

160. Significantly, other patients experienced 32%, 36%, 42% and 60% increases in their respective (R)-methadone levels.

161. The study reported that the 21% mean increase in (R)-methadone levels in study participants was “significant” but nevertheless “weak.” The study’s author hypothesized that “one or several quetiapine metabolite(s) which are produced in vivo and which are not included in the in vitro interaction study performed by AstraZeneca (AstraZeneca, data in file), are responsible for this interaction.”

162. The authors further opined “it is not expected that such a weak increase would result in clinically significant effects in relation to respiratory depression, due to the high tolerance of patients in methadone maintenance to the opioid effect of methadone.”

163. However, in a continuing medical education (“CME”) article titled “The Safe and Effective Use of Methadone in Primary Care”, Steven D. Passik, PhD. had the exact opposite opinion stating in relevant part:

“The thing about methadone I would want primary care doctors to understand more than anything is that hurting someone on methadone is very counterintuitive. It's exactly the person you think you can't hurt, the opioid-tolerant patient, because methadone is sometimes upwards of 80% more potent in an opioid-tolerant patient than it is in an opioid-naïve patient.” (emphasis added).

164. In the same CME article, Dr. Charles E. Argoff, MD also offered his opinion about how potent methadone is stating in relevant part:

“As you were saying, I was thinking of a number of patients who have converted to methadone, and I've learned with a lot of experience to respect the drug in that regard and to start much lower than I would have thought I would have started. We really have to respect the potency of the drug and not only its variability. To your point, the fact that even in opioid-tolerant patients who are usually on 60 mg of morphine or its equivalent per day, the starting [methadone dose is very low]. That's just how careful you have to be.” (emphasis added).

165. The Uehlinger authors hypothesized that the increase in (R)-methadone is attributable to quetiapine’s effect on CYP 2D6 and/or p-glycoprotein.

166. According to AstraZeneca’s September 19, 2005 Seroquel Periodic Safety Update Review, Seroquel has a “high affinity” for p-glycoprotein stating in relevant part:

cytochrome P450's involved in the metabolism of SEROQUEL. Although SEROQUEL was found to have a high affinity for ABCB1 (P-glycoprotein) transporter in vitro, pantoprazole and doxepin did not have any effect on the activity of this transporter in concentrations up to 100 uM. The authors concluded that the nature of the observed interaction remained unknown.

167. Regardless of the mechanism, the results of the study were troubling enough to lead the authors to conclude that “the present study...clearly warrant[s] future studies with larger numbers of genotyped patients to confirm these results.” To date, no such study has been conducted.

168. Furthermore, in light of the Uehlinger study, it is clear that both the Seroquel and Seroquel XR prescribing information “Pharmacokinetics” sections are not only dangerously misleading but also in fact **false** when both state that quetiapine “is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.”

169. On September 17, 2007, AstraZeneca published its annual Periodic Safety Update Report (“PSUR”) for Seroquel which included a section titled “SEROQUEL and methadone drug interaction” whose conclusion reads:

9.23.3 Overall conclusion

Following a careful review of all the reports of a possible drug interaction between SEROQUEL and methadone, it was determined that these reports do not contain any new useful information about the use of SEROQUEL. The reports describe events that can occur with methadone alone [such that the events and clinical course could be explained without a SEROQUEL/methadone drug interaction], or may reflect a known risk of overdose (death) or contained limited information. No changes to the CDS are warranted at this time regarding the concomitant use of SEROQUEL/SEROQUEL XR and methadone.

170. Interestingly, although this PSUR was issued some three months *after* the Uehlinger study was published, it makes no mention of the results of the study.

171. Furthermore, methadone’s own prescribing information advises “extreme caution is necessary when any drug known to have the potential to increase the QT interval is prescribed with methadone.”

172. As will be described *infra*, AstraZeneca argued that quetiapine has a “placebo” like effect on the QT interval as late as April 2009.

173. AstraZeneca has not only failed to disclose this potential deadly drug-drug interaction in either Seroquel or Seroquel XR’s prescribing information, it also deliberately misled physicians who have specific concerns about the concomitant use of methadone and quetiapine.

174. Physicians who have concerns or questions about the safety of an AstraZeneca product can relay their question(s) through their AstraZeneca sales representative to AstraZeneca's medical information department. A question relayed this way is known as a "Product Information Request," or PIR. AstraZeneca, in turn, sends the physician a "medical letter" that is supposed to address the physician's concerns or questions.

175. In the aforementioned "quiz" Plaintiff-Relator recently took to help with compliance with AstraZeneca's Corporate Integrity Agreement, she was asked the following question: "Which one of the following best describes a PIR question?" The correct answer to this question was: "Accurate and scientifically balanced response to a specific question."

176. Despite this representation, AstraZeneca hides the true results of study results contained in medical letters. This concealment is a direct violation of AstraZeneca's Corporate Integrity Agreement with the federal government and a violation of federal and state law.

177. On June 21, 2010 a physician in Plaintiff-Relator's territory, "Dr. John Doe," asked Plaintiff-Relator to relay a question he had about the concomitant use of quetiapine with opioids, opiates, and narcotics.

178. AstraZeneca's medical letter to "Dr. John Doe" concerning the concomitant use of methadone and Seroquel/Seroquel XR states, in relevant part:

Methadone

Uehlinger and colleagues³ studied steady-state plasma concentrations of methadone in 14 patients (>18 and <65 years of age) receiving methadone maintenance treatment who were about to start antipsychotic therapy with quetiapine. Steady-state methadone plasma concentrations were measured before and after quetiapine administration (mean dose: 138 mg/day) during a mean period of 30 days. The mean methadone dose was 121 mg/day. Eleven patients were genotyped as CYP2D6 extensive metabolizers and 3 patients were poor metabolizers. All patients were Caucasian (11 males, 3 females) and smokers. Quetiapine plasma concentrations-dose ratios were not significantly different between CYP2D6, CYP2B6, and ABCB1 genotypes. Methadone plasma levels-dose ratios were not significantly different between ABCB1 and CYP2D6 genotypes. A significant mean increase of 21% in the methadone concentration-dose ratios was observed after the administration of quetiapine in the entire group for (R)-methadone (active form of methadone) ($p=0.026$). The changes in the methadone concentration-dose ratios were not significantly different between the CYP2B6, CYP2D6, and ABCB1 genotypes. No signs of overmedication caused by increased methadone concentrations were observed or reported.

SEROQUEL

- In a study evaluating the steady-state plasma concentrations of methadone (mean dose: 121 mg/day) before and after quetiapine (mean dose: 138 mg/day) administration in 14 patients, a significant mean increase of 21% in the methadone concentration-dose ratios was observed after quetiapine administration ($p=0.026$). No signs of overmedication caused by increased methadone concentrations were observed or reported.³

179. The average dose of quetiapine in the Uehlinger study was 138 mg.

180. The lowest effective dose of quetiapine in Seroquel taken by patients with schizophrenia was 150 mg.

181. The lowest effective dose of quetiapine in Seroquel taken by patients for the acute treatment of manic episodes in Bipolar 1 disorder was 400 mg.

182. The lowest effective dose for quetiapine in Seroquel taken by patients for maintenance treatment for Bipolar 1 disorder was also 400 mg.

183. Accordingly, doses of Seroquel or Seroquel XR higher than 138 mg can cause an even greater increase in a patient's methadone level than what was reported in the Uehlinger study. **Any unexpected increase in a patient's methadone level can be fatal.**

184. Notably, the AstraZeneca medical letter makes no mention of the patient in the study that experienced an 85% increase in (R)-methadone levels. Rather, AstraZeneca purports to minimize the significance of the lethal risks by reporting only the “mean” of 21%, followed by the false and misleading statement that, “no signs of overmedication caused by increased methadone concentrations were observed or reported” notwithstanding the fact that an 85% increase was actually “observed” and “reported” in the study. Additionally, the study did not measure what happened to the study participants when Seroquel was discontinued. This failure ensured that there was no measurement of whether the patients experienced “withdrawal symptoms” when Seroquel was discontinued.

185. AstraZeneca’s failure to disclose this 85% increase in (R)-methadone levels in either a medical letter to physicians, or in either Seroquel or Seroquel XR’s package inserts, was reckless and has caused methadone patients to be harmed and, in some cases, suffer fatal overdoses of methadone.

186. **Importantly, in its letter to Dr. Doe, despite knowing of the risks of using Seroquel with other drugs known to increase the QTc interval, AstraZeneca failed to warn of the increased risk of QTc prolongation, cardiac arrhythmias, and Torsades de Pointes when Seroquel is used with methadone.**

187. As in Dr. John Doe’s case, from at least 1997 onwards, AstraZeneca failed to alert State Drug Utilization Review Boards of the dangers associated with using quetiapine with other drugs (including methadone) that cause increases in the QTc interval.

188. Furthermore, AstraZeneca failed to warn Dr. Doe about the January 2010 label change that advised “caution” when Seroquel was used with drugs like methadone that are known to cause increases in the QT/QTc interval.

189. The July 2007 Uehlinger study called for a specific study to measure quetiapine's effect on methadone stating that the QT/QTc prolonging effect of quetiapine next to methadone "must...clearly be examined along with the use of higher quetiapine doses." To date, no such study has been conducted.

190. In March 2010, the MEB found that "quetiapine has shown some potential to increase QTc next to methadone, by which combination could lead to a potentially dangerous situation as is currently warned for in section 4.5 of the SPC (Summary of Product Characteristics). In addition, as many of the reported cases had a fatal outcome, the MAH (Market Authorization Holder – AstraZeneca) should continue to monitor the interaction closely."

191. Consequently, AstraZeneca knew that "quetiapine has shown some potential to increase QTc next to methadone" and that "many of the reported cases had a fatal outcome" in March 2010, but failed to alert Dr. John Doe about this information.

192. Although the MEB stated that the danger of using quetiapine with methadone "is currently warned for" in quetiapine's product labeling, there was no specific warning about the risks of the concomitant use of the two drugs until June 2011. Furthermore, the quetiapine label in Europe (where the Dutch regulatory authority was based) had a warning advising "caution" when quetiapine was used alongside other drugs known to increase the QTc interval from February 2006 onwards.

193. Furthermore, from 2000-2010, Los Angeles Coroner reports indicate that at least 84 people died with both methadone and quetiapine in their system.

194. From 2007-2011, Wayne County, Michigan Medical Examiner (Detroit) reports indicate that 41 people died with both methadone and quetiapine in their system.

195. From 2003-2010, San Diego Coroner reports indicate that 40 people died with both methadone and quetiapine in their system.

196. From 2005-2010, Pasco and Pinellas County (Florida) Medical Examiner reports indicate that 33 people died with both methadone and quetiapine in their system.

197. Of note, in January 2010, *Pharmacy Times* published an article titled “Drug Interactions: Safely Using Quetiapine.”

198. The authors of the study offered their unbiased opinion of the results of the Uehlinger study. Their comments on the Uehlinger study read in their entirety:

Methadone

In a study of patients stabilized on methadone, the addition of quetiapine produced a modest increase in the active (R)-methadone plasma concentrations.⁸ Although the effect was not large, there was considerable variability among the patients; it is possible that some patients would be adversely affected.

199. Thus, an unbiased review of the study concluded that it is at least “possible” that patients taking both methadone and quetiapine could “be adversely affected.”

200. Yet, when patients take methadone, any increase in methadone levels is considered clinically significant and potentially fatal. In fact, Dolophine, a branded version of methadone, contains a black box warning of this risk that reads in relevant part:

WARNINGS:

Keep DOLOPHINE out of the reach of children. Accidental overdose by a child is a medical emergency and can result in death. If a child accidentally takes DOLOPHINE, get emergency help right away.

Do not take a higher dose of DOLOPHINE or take it more often than prescribed. This can lead to an overdose and possible death.

201. In effect, when quetiapine is used concomitantly with methadone, it can cause the patient to receive a “higher dose” of methadone, which, in turn, “can lead to an overdose and possible death.”

202. Thus, AstraZeneca has ensured that when a physician prescribes methadone concomitantly with quetiapine, the physician has no knowledge that a patient's (R)-methadone levels can increase up to 85%. This increase can lead the patient to experience methadone overdose and possible death.

203. Furthermore, AstraZeneca is aware that both Seroquel and Seroquel XR are prescribed by physicians for off-label purposes in patients taking methadone. Specifically, AstraZeneca knows that Seroquel and Seroquel XR are prescribed off-label to treat anxiety and/or sleep disorders in patients taking methadone as part of a methadone maintenance treatment program or for pain. The use of Seroquel and Seroquel XR for anxiety and/or sleep disorders is not supported by the ASHS Compendia.

204. Nevertheless, AstraZeneca directs its sales representatives to sell and provide samples to physicians it knows prescribes both Seroquel and Seroquel XR for these off-label and highly dangerous uses.

E. Seroquel's effect on the QT/QTc interval and AZ's violation of Federal laws

205. The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. In general, the QT interval represents electrical depolarization and repolarization of the left and right ventricles. **A prolonged QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes ("TdP") and a risk factor for sudden death and cardiac arrest.**

206. A study published in October 2014 titled, "Antipsychotics and Associated Risk of Out of Hospital Cardiac Arrest" reviewed cases of "out of hospital cardiac arrest" in patients taking typical and atypical antipsychotics in Denmark from 2001-2010.

207. The study found that of all the atypical antipsychotics only patients taking quetiapine had an increased risk of suffering an out of hospital cardiac arrest.

208. The odds ratio for patients taking quetiapine and “out of hospital cardiac arrest” was 3.64. This result was statistically significant.

209. One of the ways Seroquel affects the QT interval is by blocking the IKr potassium channels which leads to delayed repolarization of the heart.

210. Prolongation of the QT interval corrected for heart rate is called the QTc interval.

211. For each 10 millisecond increase in the QTc interval, there is a 5%-7% increase in the risk of developing Torsades de Pointes.

212. According to the European Medicines Agency, every 20 millisecond increase in the QTc interval “substantially increases the risk of TdP.”

213. When one drug with QTc prolonging effects (like quetiapine) is combined with another QTc-lengthening drug, the concomitant use has additive or even **potentiating** effects.

214. Typical symptoms of QTc prolongation are tachycardia (rapid heartbeat), syncope (a sudden loss of consciousness), near syncope, chest pain, hypotension (low blood pressure), dizziness, light-headedness, seizure (due to cerebral hypoxia), palpitations, dyspnea (shortness of breath), TdP and sudden death.

215. In most instances, there is no warning prior to syncope precipitated by QTc prolongation.

216. According to the FDA, “[t]here is a high rate of syncope and syncope related events” in healthy volunteers taking quetiapine.

217. Sudden cardiac death accounts for 300,000 to 400,000 deaths annually in the United States.

218. The prospective, population-based Rotterdam Study found that, independent of other known risk factors, prolongation of the heart-rate corrected QT (“QTc”) interval increased the risk of sudden cardiac death (SCD) in adult patients by 60%.

219. Another analysis of the Rotterdam Study found that an abnormally prolonged QTc was associated with an **eightfold increase** in the risk of sudden cardiac death in persons below the age of 68.

220. From the time that Seroquel was first commercially available in 1997 through January 2010 – the date of the first Seroquel United States warning related to QTc prolongation – there were 520 cases of QTc prolongation, TdP and/or cardiac arrest associated with quetiapine usage. **Nearly 60% of these cases were fatal.**

221. Prior to June 2011, there was no warning in either Seroquel label concerning the risk of sudden cardiac death associated with the use of quetiapine. Now the label reads in relevant part:

The use of quetiapine should be avoided in combination with other drugs that are known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone).

Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsade de pointes and/or sudden death including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

Caution should also be exercised when quetiapine is prescribed in patients with increased risk of QT prolongation (e.g., cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure and heart hypertrophy).

222. For men, QTc prolongation greater than 450 ms is considered “abnormal.” For women, QTc prolongation greater than 470 ms is considered “abnormal.” QTc values greater than 500 ms are considered prolonged and are associated with an increased risk of arrhythmias, including TdP.

223. During the entire time quetiapine has been on the market, AstraZeneca has maintained a “Core Data Sheet” (“CDS”). The CDS has alternatively been known as the Core Product Information or Company Core Data Sheet (“CCDS”).

224. AstraZeneca defines the CDS as a “summary of the company’s position with respect to essential scientific information, recommendations, and instructions needed for the safe and effective use of the product.” Furthermore, “[i]t serves as the master document for regular implementation of material changes in local prescribing texts” including the Seroquel label in the United States.

225. By definition, anything that is in the CDS should also be in the product’s United States labeling.

226. On May 28, 2008, Dr. Martin Brecher, the medical science director for AstraZeneca testified in a deposition what the core data sheet is. His deposition testimony reads in relevant part:

7 Q. What is the core data sheet?
8 A. The core data sheet is the
9 best description of the safety profile of
10 the drug and represents the core items
11 that have to be included in every product
12 label. So it’s that -- those facts about
13 the safety of the drug that must be
14 included in every label around the world.

227. Consequently, according to AstraZeneca's own medical science director, "the core data sheet is the best description of the safety profile of the drug and represents the core items that have to be included in every product label. So it's that – those facts about the safety of the drug that **must be included** in every label around the world."

228. AstraZeneca has known since at least 1995 that Seroquel prolongs the QTc interval at **therapeutic doses**.

229. AstraZeneca has known since at least July 1997 that the United Kingdom's Medicines Health Regulatory Authority required that the quetiapine label advise "caution" when quetiapine is used with other QT/QTc prolonging medications especially in the elderly.

230. Instead of changing the Seroquel labels to include a warning that the use of quetiapine with other drugs that prolong the QT/QTc interval is dangerous, AstraZeneca **fraudulently concealed** this danger from State Drug Utilization Boards, and others, in order to reap greater sales of quetiapine.

231. A study published in the *Journal of Clinical Psychopharmacology* in 1996 showed that quetiapine increased the QTc interval 8 milliseconds ("ms") versus **placebo**. These results were statistically significant.

232. Despite this finding, in a document titled "Formulary Submission Dossier" submitted to the state of Montana's Department of Public Health & Human Services dated June 4, 2009, AstraZeneca was **silent** about the QT prolongation safety findings of this study:

Safety:

No significant differences in occurrence of EPS between SEROQUEL and placebo. No

significant difference in prolactin levels between SEROQUEL and placebo. Somnolence, agitation, headache most commonly reported. Elevated LFT's, postural hypotension, and weight gain also reported.

233. A study published in 1997 in *Biological Psychiatry* found that a 600 mg dose of quetiapine increased the QTc interval 13 ms versus placebo.

234. Despite this finding, in a document titled "Formulary Submission Dossier" submitted to the state of Montana's Department of Public Health & Human Services dated June 4, 2009 AstraZeneca was silent about the QT prolongation safety findings of this study:

Safety:

No significant differences in occurrence of EPS between SEROQUEL and placebo. No significant difference in prolactin levels between SEROQUEL and placebo. Somnolence, agitation, headache most commonly reported. Elevated LFT's, postural hypotension, and weight gain also reported.

235. In regulatory filings and information submitted to State Drug Utilization Review Boards, AstraZeneca has repeatedly stated that quetiapine's effect on the QT/QTc interval is equivalent to haloperidol's effect on the QT/QTc interval that is equivalent to placebo (sugar pill).

236. Yet, in 1997, a study in the *Archives of Internal Medicine* study reported Torsades de Pointes with low dose haloperidol.

237. On June 13, 1997, the FDA's review of AZ's New Drug Application for Seroquel reported the following:

1. For Study 0013, a statistically significant increase of 10 milliseconds in the 600 mg arm of the study.
2. For Study 0015, four patients in the quetiapine 600 mg group had treatment emergent QTc greater than or equal to 500 ms compared to one each in the 300 mg and 75 mg groups and **none** in the haloperidol group.
3. FDA determined that, "on balance, the data do not consistently reflect a QT/QTc prolonging effect of quetiapine."

238. In **July 1997**, the Seroquel "Summary of Product Characteristics" ("SPC") is approved in the United Kingdom. The SPC contained warnings mandated by the United Kingdom's Medicines and Healthcare products Regulatory Agency ("MHRA") concerning the concomitant use of quetiapine with other QTc prolonging agents that read:

4.4 Special Warnings and Special Precautions for Use

Cardiovascular disease

In clinical trials, quetiapine was not associated with a persistent increase in QT_c intervals. However, as with other antipsychotics, caution should be exercised when quetiapine is prescribed with drugs known to prolong the QT_c interval, especially in the elderly.

9. Date of First Authorisation/Renewal of Authorisation

31 July 1997

239. As the United Kingdom label indicated, Seroquel's effect on the QTc interval in the **elderly** is particularly dangerous. This warning would prove prescient in light of the "black box" warning that the FDA imposed on the United States Seroquel label concerning its use in

patients with dementia in August 2008, or over eleven years after the United Kingdom warned of such a risk.

240. The SPC also advised that Seroquel “may cause prolongation of the QTc interval”:

4.8 Undesirable effects

As with other antipsychotics, SEROQUEL may cause prolongation of the QTc interval, but in clinical trials, this was not associated with a persistent increase (see *Section 4.4 Special warnings and special precautions for use*).

241. In 1998, Dr. Silvia G. Priori stated in the *Journal of Cardiovascular Electrophysiology*:

‘Almost every week a new agent is added to the list of drugs associated with acquired long QT syndrome (LQTS) and torsades de pointes (TdP). Despite this impressive number of reports, the awareness of this subject is still limited among medical professionals and ... It is likely that prevention of drug-induced TdP will never be fully successful, because it is a moving target. A patient may not be at risk when therapy is initiated, and may become at risk 5 days later because ... It is intuitive that when two or more agents sharing potassium-channel-blocking activity are simultaneously administered, the risk of excessive prolongation of repolarization is substantially increased ... The exclusion of potassium-channel-blocking properties might be considered in the future as a requirement before new molecules are approved for marketing, and more strict warnings in the package insert of drugs with known repolarization prolonging activity could be enforced.’

242. The United States Seroquel labels had no warning concerning the risks inherent in a patient taking quetiapine – an agent known to have potassium-channel blocking activity and effects on the QTc interval – with other agents with known potassium-channel blocking activity and effects on the QTc interval until January 2010 when AstraZeneca belatedly, and unilaterally, changed the label pursuant to the Changes Being Effected regulation.

243. Each year, an estimated \$177.4 billion is spent to address the treatment failures and new medical problems that are generated by adverse drug events including adverse drug events caused by the concomitant use of quetiapine with other drugs known to increase the QT/QTc interval.

244. On April 27, 2000, a “special article” titled “The potential for QT prolongation by non-anti-arrhythmic drugs: Clinical and regulatory implications – Report on a Policy Conference on the European Society of Cardiology” was published in the journal *Cardiovascular Research*.

245. The authors of this “special article” included cardiologist experts from across the world. The authors identified haloperidol as a drug that both increased the QT/QTc interval and caused Torsades de Pointes.

246. In 1999, the FDA authorized Pfizer to conduct Study 054. Study 054 was a study comparing the effects of thioridazine, haloperidol, ziprasidone, risperidone, olanzapine, and quetiapine on the QTc interval.

247. In a memorandum dated June 14, 2000, FDA physician Dr. Maryann Gordon stated “it is generally accepted, perhaps erroneously, that [haloperidol’s] effect on QTc is not different from placebo.”

248. In a memorandum dated June 20, 2000 from the FDA’s Dr. Thomas Laughren stated “we [FDA] have an abundance of data from multiple independent development programs

showing no difference between haloperidol (at the oral dose used in study 054) and placebo on QTc.”

249. For its part, Pfizer, Study 054’s sponsor, stated that there was a “relationship between concentration and QTc effect...for haloperidol, **providing evidence of the capacity of that drug to prolong QTc at a therapeutic dose.**”

250. As will be shown *infra*, Dr. Gordon, Pfizer, and the scientific community were prescient about haloperidol’s effect on the QT/QTc interval.

251. On July 19, 2000, the results from Pfizer’s Study 054 were made publicly available and showed:

1. Quetiapine increased the QTc interval 14.5 ms. In contrast, haloperidol increased the QTc interval 4.7 ms.
2. With a metabolic inhibitor present, quetiapine increased the QTc interval 19.7 ms. In contrast, haloperidol increased the QTc interval 8.9 ms with a metabolic inhibitor present.
3. For one period, 15% of the quetiapine subjects had ≥ 60 ms increases in the QTc interval. In contrast, no risperidone, olanzapine or haloperidol patients had ≥ 60 ms increases in their QT interval.
4. Pfizer concluded “a relationship between concentration and QTc was detected for haloperidol (in the study), providing evidence of the capacity of that drug to prolong QTc at a therapeutic dose.”

252. In August 2000 a study was published in the *European Heart Journal* that identified **haloperidol** as a drug that **associated with Torsades de Pointes and increases in the QTc interval.**

253. On December 18, 2000, AZ’s Seroquel Strategy document was published internally at AZ.

254. The document identified “**no clinically significant QTc prolongation**” as a “**Key Claim**” for Seroquel.

255. The document further identified “**Defend against potential FDA label threats: QTc and diabetes**” as a “**Key Success Factor.**”

256. The document reads in relevant part:

‘Seroquel’ Strategy Summary

Last Update: 18/12/2000

Key Claims

Current Claims
At least as efficacious as other first line atypicals (olanzapine/risperidone)
More effective than haloperidol and chlorpromazine (typical antipsychotics)
Effective at controlling depressive symptoms and improving cognition
Superior tolerability to typicals and first line atypicals
Weight neutral, placebo level EPS and prolactin levels, and <u>no clinically significant QT prolongation</u> →

Key success factors

	Key Success Factor	Required Actions	Risk/Urgency	Responsible
1	Maintain competitive SoV	Increased S and CNS experienced manpower, both globally and MCs	M/H	SET MCP GPT
2	Delivery of compelling data into marketplace ↓	Publication/communication of data to support stronger efficacy message and to differentiate on superior tolerability via: Data mining, clinical trials, comparative data, IITs	L/H	GPT
3	Broaden Seroquel use on and off label	Utilise whole selling team. Educational programmes to share off label data.	L/H	MC
4	Maintain competitive label	Successfully deliver LCM programme: Granules 2002 Sustained Release 2003 Bipolar Disorder 2003/4 Remove eye monitoring from US label. Defend against potential FDA label threats: QTc, diabetes. ←	M/H	GPT
5	Communicate efficacy at the right dose	Communicate clear dosing guidelines and data. Promote starter pack. SR formulation.	L/H	GPT MC

257. Consequently, as early as December 12, 2000 if not sooner, AstraZeneca identified a “Key Success Factor” for its Seroquel brand as defening against potential FDA labels threats related to QTc prolongation and to “maintain a competitive label.” The group responsible for this “Key Success Factor” as the GPT, or Global Product Team. The “Risk/Urgency” of this “Key Success Factor” was “M/H”, or medium/high:

Key success factors

	Key Success Factor	Required Actions	Risk/Urgency	Responsible
4	Maintain competitive label	Successfully deliver LCM programme: Granules 2002 Sustained Release 2003 Bipolar Disorder 2003/4 Remove eye monitoring from US label. Defend against potential FDA label threats: QTc, diabetes.	M/H	GPT

258. As will be shown *infra*, AstraZeneca was successfully able to “defend against” the “label threats” related to QTc prolongation posed by the Food and Drug Administration for 126 months, or **for over ten years.**

259. During that ten-year period, State Medicaid agencies approved, and paid for, quetiapine prescriptions filled concomitantly with other drugs known to increase the QT/QTc interval **under the false premise that such concomitant use was safe.**

260. AstraZeneca periodically issued Periodic Safety Update Reports (“PSUR”) to the FDA and other pharmaceutical regulatory agencies worldwide including the Dutch MEB.

261. The MEB was the regulatory agency in charge of monitoring the quetiapine label for the European Union. The MEB issued its own analysis of each AstraZeneca Seroquel/Seroquel XR PSUR in an assessment report.

262. On February 20, 2001, AstraZeneca published an internal document titled “AstraZeneca SEROQUEL ® PROLONGED QT INTERVAL CHECKLIST.”

263. The document was designed to distribute to medical professionals who reported QT/QTc prolongation with Seroquel.

264. The “Associated Signs/Symptoms” of QT/QTc prolongation were defined as “Palpitations,” “Dizziness,” “Syncope,” “Cardiac Arrest,” “Death,” and “Other”.

265. Physicians were also asked whether Seroquel was “rechallenged” to decide whether there was a reoccurrence of QT/QTc prolongation while on Seroquel.

266. As will be shown *infra*, patients who developed QTc prolongation while on Seroquel (including United States active duty military personnel and Medicaid beneficiaries) exhibited a “positive dechallenge” where the QTc prolongation resolved when the Seroquel was discontinued.

267. According to the FDA, a positive dechallenge is “a partial or complete disappearance of an adverse experience after withdrawal of the suspect product.”

268. Lastly, physicians were asked whether there was a “reasonable possibility that the drug [Seroquel] may have caused the abnormality (QT/QTc prolongation).”

269. On or about February 26, 2001, the results of Study 93 were reviewed and analyzed by the FDA. Although the FDA concluded that Study 93’s “study design and interpretation of its results were hampered by the lack of a control group,” **Study 93 nevertheless showed that Seroquel increased the QTc interval by 22 ms.**

270. In a March 2001, AstraZeneca representatives used a “Speakers Slide Kit” to educate physicians about Seroquel. In this document, AstraZeneca made the following representations about Seroquel’s effect on the QTc interval:

Seroquel - no clinically significant effect on cardiac repolarisation (QT interval)

- **No statistically significant Seroquel / placebo differences in proportion of patients experiencing potentially important changes in ECG parameters in placebo-controlled trials**

271. On March 7, 2001, the first patient was enrolled in Study 41. Study 41 was a multi-center, randomized, placebo-controlled study to determine the effects of Seroquel XR on schizophrenic patients.

272. Prior to the first enrollment of patients in Study 41, the AstraZeneca clinical study team amended the exclusion criteria for the study.

273. The protocol read as follows:

Table 13 Protocol amendments			
Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated amendment ¹
	The exclusion of patients with a QT _c interval longer than 500 msec, as calculated using the Fridericia correction, was removed (not applicable).	Unnecessary exclusion, per recent clinical data	AstraZeneca clinical study team

274. Consequently, based upon “recent clinical data,” the “AstraZeneca clinical study team” removed the exclusion criteria that included “patients with a QT_c interval longer than 500 msec” because they deemed it “[u]nnecessary per recent clinical data.”

275. As will be shown *infra*, on September 30, 2002, AstraZeneca would exclude patients who had QT_c interval >450 msec in trial 49. Upon information and belief, as in Study 41, this exclusion criterion was predicated on “recent clinical data.”

276. Dr. Robert Reinstein was an AstraZeneca paid speaker who collected over \$450,000 in speaking fees from AstraZeneca from 1997 through 2007.

277. In June 2001, Dr. Reinstein was paid to speak about Seroquel to over 5,000 physicians and health care workers across the country.

278. Dr. Reinstein made the following statements about Seroquel and QTc prolongation to the participants:

7 MR. REINSTEIN: It's well tolerated.
8 Patients don't get EPS with the high dosing. They don't
9 get problems with the prolactin levels. They don't get
10 problems with the widening of the QTc interval on EKG
11 and they don't get weight gain. So it's a very well
12 tolerated drug in high dosing.

25 DR. MAGENDER: Do you think that -- do you
0036

1 think that ziprasidone with other antipsychotic
2 medications like Seroquel, does it have any cumulative
3 effect on QTc interval?

4 MR. REINSTEIN: Actually, Dr. Magender,
5 we've tried every drug combination. We actually have
6 some patients on Ziprasidone and Seroquel -- Quetiapine.
7 We've been monitoring the QTc interval. And we've not
8 found any significant problems with the combination of
9 Ziprasidone and Quetiapine.

10 It's sort of an interesting combination.
11 ziprasidone seems to be a more stimulating kind of drug
12 for the negative symptoms. And Seroquel seems to work
13 better for some of the positive symptoms and the
14 anxiety. So it's an interesting combination. We
15 actually have some patients on it and we're not seeing
16 any problems with it with the QTc interval.

279. These comments were reckless and amounted to AstraZeneca promoting a use of Seroquel with a drug that placed patients at great risk of sudden cardiac death and other cardiac effects.

280. In fact, the June 2011 Seroquel label specifically lists ziprasidone as a drug whose use "should be avoided" with Seroquel.

281. On October 23, 2001, Dr. Raymond Woosley, a prominent researcher and expert on the treatment of arrhythmias and the cardiac toxicity of drugs, published a list of drugs known to prolong the QT/QTc interval that included **quetiapine**. Dr. Woosley has periodically updated his list over the years and quetiapine remains on it.

282. Interestingly, Dr. Woosley was a co-author with Stots Reelee, a senior AstraZeneca employee who was a member of the Seroquel Product Team, on at least **sixteen separate studies** and abstracts including papers dedicated to the study of **refractory arrhythmias, ventricular arrhythmias and ventricular tachycardia**. Each of these adverse events is associated with QTc prolongation.

283. In July 2002, the Japanese label for Seroquel had specific warnings about Seroquel's effect on heart rhythms and a specific warning about the risk Seroquel posed for sudden death:

(2) Other Adverse Reactions

1) Adverse reactions from Japanese clinical studies

Cardiovascular	Tachycardia	Hypotension postural, palpitation, hypotension, hypertension, bradycardia, arrhythmia, syncope, electrocardiogram abnormal
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10. Other cautions

- (1) Sudden death from an unknown cause was reported during the treatment with this product.
- (2) Myocardial infarction and gastric ulcer haemorrhagic of which the causality with this product is unknown were reported in the Japanese clinical studies. Acute renal failure was reported in the Western long term study used for the submission.

284. On September 14, 2002, a PSUR was issued for Seroquel. The PSUR reported eleven cases of QTc prolongation with Seroquel as well as one positive dechallenge. According to the FDA, a positive dechallenge is "a partial or complete disappearance of an adverse experience after withdrawal of the suspect product."

285. The September 14, 2002 PSUR also reported the following cases in detail:

██████████: This report of "Electrocardiogram QT corrected interval prolonged" described a ██████████ who was receiving Seroquel (750 mg/day; indication unknown). After four to five weeks of Seroquel therapy a routine ECG detected a QTc of 1.06 seconds. No pretreatment ECG had been carried out. The physician decided to reduce the dose of Seroquel to 400 mg/day and do a repeat ECG. The patient was referred to a cardiologist. Following a second ECG, the first QTc interval of 1.06 seconds was noted to have been miscalculated. However, it was unclear whether or not the patient had still experienced a prolonged QTc interval. The QTc value for the second ECG was not provided. No medical history was reported and the patient was not receiving any concomitant medication. Previously, she had received unsuccessful treatment with risperidone and amisulpride. No further information was provided and additional information has been requested.

██████████: This report of "Electrocardiogram QT corrected interval prolonged" described an adult male patient (age unknown) who was receiving Seroquel (dose/duration unknown) for the treatment of psychosis. During a routine ECG it was discovered that the patient's QTc interval was >0.5 (units not provided). (No pretreatment QTc interval was provided.) The patient also experienced tachycardia and sweating. Seroquel was

██████████ This serious report of "Electrocardiogram QT prolonged" described a male patient (age unknown) who was receiving Seroquel (600 mg/day; duration and indication unknown) and experienced QT prolongation (no values provided). The patient was receiving concomitant medications (not specified), but had not experienced the event prior to the initiation of Seroquel. Medical history was not reported. Follow up information has been requested.

██████████ This serious report of "Electrocardiogram QT prolonged" described a ██████████ patient who was receiving Seroquel (25 mg/day) for the treatment of psychosis. The patient took two doses of Seroquel and experienced feeling achy, hypotension with bradycardia, sinus rhythm, and prolonged QT interval (no value provided). Seroquel was discontinued and the patient recovered five days later. Medical history included coronary artery disease, agitation, nausea, dementia, myocardial infarction, and Parkinson's disease. Concomitant medications included aspirin, Elantan (isosorbide), diazepam, domperidone, Madopar (levodopa), trimethoprim, and co-trimazine. No further information was provided and additional information is not available.

██████████ This serious report of “Electrocardiogram QT prolonged” described an ██████████ patient who was receiving Seroquel for the treatment of confusion. Seroquel was gradually increased to 100 mg/day, and after two weeks of treatment the patient developed “cardio-respiratory arrest” and a prolonged QT interval (no value provided). Seroquel was discontinued and the events resolved the same day, without CPR. Medical history included coronary artery disease, prostatic cancer, and Parkinson's disease. Concomitant medications included dexamethasone, Madopar (levodopa), aspirin, metoprolol, isosorbide, venlafaxine (labeled for prolonged QT interval), senna, and omeprazole. No further information was provided and additional information is not available.

██████████ This serious literature report of “Electrocardiogram QT prolonged” described a ██████████ patient who was receiving Seroquel (800 mg/day) and sertraline (100 mg/day, labeled for prolonged QT) for the treatment of schizophrenia. An unknown time after starting these medications, routine lab screening revealed dyslipidemia (cholesterol 237 mg/dl; triglycerides 172 mg/dl). Lovastatin (10 mg/day) was prescribed. Two months later the lipid levels were improved (cholesterol 178 mg/dl; triglycerides 114 mg/dl), however a routine ECG demonstrated a prolonged QTc interval of 569 msec. On the day of the ECG the patient reported she had taken lovastatin 20 mg because she had missed a dose. Lovastatin was reduced to 5 mg/day and a repeat ECG the following day indicated that the patient's QTc

interval had returned to the patient's baseline of 424 msec. Two months later the patient's lipids had again increased and she was switched from lovastatin to niacin. Subsequent ECGs indicated normal findings. Medical history included dyslipidemia. No other concomitant medications were reported. The authors hypothesize that the addition of lovastatin caused an increase in the plasma Seroquel levels secondary to inhibition of the cytochrome P450 3A4 isoenzyme. (Lovastatin is an inhibitor of CYP 3A4). This report is contained in the Drug Interaction section 9.5.

██████████ This non-serious report of “Electrocardiogram QT prolonged” described a ██████████ patient (age unknown) who experienced prolonged QT interval (no value given) while on therapy with Seroquel. Medical history included anorexia, hypokalemia, and anxiety. No outcome or any other information was provided. Follow up information has been requested.

286. Importantly, one of these narratives identifies a patient who experienced QTc prolongation while taking quetiapine with venlafaxine (a drug AstraZeneca itself identified as a QT/QTc prolonging drug).

287. This narrative described a “positive de-challenge” between quetiapine and QTc prolongation for two separate patients:

three reports were confounded by concomitant illness: [REDACTED] (ischemic heart disease), [REDACTED] (coronary artery disease, myocardial infarction) and [REDACTED] (coronary artery disease). [REDACTED] was also confounded by a concomitant medication (venlafaxine) labeled for prolonged QT interval, but it did describe a temporal relationship (two weeks after Seroquel started) and a positive de-challenge (event stopped the day Seroquel was discontinued). [REDACTED] described a temporal relationship between the event and the first two doses of Seroquel. And a positive de-challenge was described in the report. [REDACTED] described a positive de-challenge.

288. Additionally, AstraZeneca concluded that there was “insufficient evidence exists to suggest that therapeutic doses of Seroquel can cause prolongation of the QT interval”:

Following a careful review of these reports, it was determined that insufficient evidence exists to suggest that therapeutic doses of Seroquel can cause prolongation of the QT interval.

289. On September 30, 2002, Study 49 enrolled its first patient. Any patient with a $QTc \geq 450$ msec was excluded from the study.

290. On November 15, 2002, the FDA issued the “CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS – A Preliminary Concept Paper – For Discussion Purposes Only.” The document advised that labeling for drugs “that affect cardiac repolarization to an extent that is considered a clinical concern” should include “discouragement (or contraindication of) the concomitant use of two or more QT/QTc interval prolonging drugs.”

291. Although “preliminary” and “for discussion purposes only,” this suggested labeling explains why AZ strongly resisted the classification of quetiapine as a drug that affects “cardiac repolarization to an extent that is considered a clinical concern” for the entirety of the time Seroquel has been on the market in the United States. For if the quetiapine labels had been rightly classified quetiapine as such a drug, the quetiapine labels would have included language

that would have advised that “the concomitant use of two or more QT/QTc interval prolonging drugs” should be **avoided** (as the label reads now).

292. Furthermore, this document, and the subsequent looting of State Medicaid programs that will be described *infra*, explains why “defend[ing]” the quetiapine label against an FDA QTc “label threat” was described as a “Key Success Factor” for the **commercial** success of the Seroquel brand.

293. In January 2003, a study comparing quetiapine and olanzapine was initiated in Canada.

294. The study, “**sponsored by AstraZeneca**” and titled “Effects of quetiapine and olanzapine in patients with psychosis and violent behavior: a pilot randomized, open-label, comparative study” contained the following exclusion criteria:

Disclosure

This research was an investigator-initiated trial sponsored by AstraZeneca (Study code: 5077-9056, granted to GD); GG

ine devices, tubal ligation). Other clinical exclusion criteria were clinically significant electrocardiography abnormality at screening; a QTc greater than 450 milliseconds or administration of medications that prolong the QT interval; known

295. Thus, in an AstraZeneca funded study patients were excluded if their QTc was greater than 450 milliseconds or if they were taking “medications that prolong the QT interval.”

296. It would be eight and a half years, or June 2011, before the United States Seroquel label would warn that the use of Seroquel with other medications that the QT/QTc interval “should be avoided.”

297. At the time Study 5077-9056 enrolled its first patient, AstraZeneca knew there was “reasonable evidence of an association of a serious hazard” with taking quetiapine with other QT/QTc prolonging medications.

298. AstraZeneca’s knowledge of the “reasonable evidence of an association of a serious hazard” with taking quetiapine with QT/QTc prolonging medications triggered its duty to amend the quetiapine label to include new warnings by a Changes Being Effected (“CBE”) supplement about the concomitant use of quetiapine with other QT/QTc prolonging medications.

299. Rather than submit such a “CBE” label change in January 2003, AZ “defended” its label and delayed such a label change until January 15, 2010.

300. On January 16, 2003, the MEB report for Seroquel was issued. The document reported two cases of positive dechallenge for Seroquel and QTc prolongation. The document also reported three cases of QTc prolongation with patients taking Seroquel alongside a QT/QTc prolonging drug.

301. Additionally, and importantly, the MEB asked AstraZeneca to add a new warning in its European labels related to quetiapine and QT prolongation in overdose. The January 16, 2003 MEB report reads in relevant part:

- Cardiac arrhythmia: There were 2 reports of 'electrocardiogram QT corrected interval prolonged' and 11 reports of 'electrocardiogram QT prolonged'. The cases can be subdivided as follows: 4 cases of QT prolongation with an overdose of quetiapine. Three cases of patients with a history of cardiovascular illnesses, two of these patients had a positive dechallenge. Three cases in which the patients received concomitant medication known to cause QT prolongation or induces increased levels of quetiapine. There was one report in which the QT was miscalculated. The MAH concludes that there is insufficient evidence to suggest that therapeutic doses of quetiapine can cause QT prolongation.

Assessor's comment: The conclusion of the MAH is endorsed, however due to the fact that in four cases of overdose and one case in which concomitant medication caused an increased level of quetiapine, QT prolongation was observed, the MAH should mention the risk of QT prolongation in section 4.9 'Overdose' of the SPC.

CONCLUSIONS

Assessment of the documents *Periodic Safety Update Report for Seroquel® (quetiapine fumarate)*. Period covered 01 August 2001 to 31 July 2002 (dated 14/9/2002, signed by [REDACTED]) led to the following conclusions:

The MAH should amend the SPC for the following issues:

- Section 4.8 Undesirable effects:
 - ✓ Headache, nausea and vomiting frequently reported in studies in adolescents,
 - ✓ Hyperprolactinaemia,
 - ✓ Tardive dyskinesia, akathisia and dystonia, and
 - ✓ Steven Johnson Syndrome.
- Section 4.9 Overdose

The risk of QT-prolongation with overdose.

302. In 2004, Drs. A. John Camm, Marek Malik, and Yee Guan Yap authored the treatise Acquired Long QT Syndrome. In this treatise, the authors stated, "TdP may masquerade as syncope, fainting, palpitations, ventricular tachycardia or sudden death."

303. Furthermore, Drs. Camm, Malik and Yap advised:

"In clinical practice, adverse effects of QT prolongation secondary to drugs can be prevented by not exceeding the recommended dose, avoiding their use or restricting the dose in patients with pre-existing heart disease or risk factors or other acquired long QT syndrome, previous ventricular arrhythmias, and/or electrolyte imbalance such as hypokalemia. **Concomitant administration of drugs** that inhibit the cytochrome P450 3A4 (e.g., imidazole antifungals, macrolide antibiotics) **or those that can prolong the QT interval** or drugs that cause hypokalemia **should be avoided**."

304. In their treatise, Drs. Camm, Malik and Yap identified quetiapine as a drug that prolongs the QT interval.

305. Furthermore, Drs. Camm, Malik and Yap identified haloperidol as having “High torsadogenic potency” with “[d]ocumented QT prolongation and cases of TdP at therapeutic doses/concentration by the drug alone in absence of QT-prolonging drugs or risk factors.”

306. On April 29, 2004, the first patient was enrolled in an AstraZeneca funded and administered study titled “Study 125.”

307. The study had “exclusion criteria” which limited which patients could participate in the study:

Study dates:

First patient enrolled: 29 April 2004

Last patient completed: 24 October 2005

Phase of development:

IV

5.3.2 Exclusion criteria

17. Patients with a known arrhythmia or $QTc \geq 450$ msec (according to Fridericia correction for heart rate (Puddu et al 1988)) or other ECG result considered to show clinically significant abnormality as determined by the investigator, in order not to jeopardize the patient safety.

308. At the time, there was no warning – whatsoever – in the Seroquel prescribing information that the use of Seroquel in patients “with a known arrhythmia or $QTc \geq 450$ ” would “jeopardize patient safety.”

309. There was also no reason provided by AstraZeneca what changed between March 2001 (where it was acceptable for patients in Study 41 to have $QTc \geq 500$ msec) and April 2004 when any patient with a $QTc \geq 450$ ms safety would be “jeopardized” if he/she was enrolled in the study.

310. Under applicable federal law, the rationale for excluding patients from Seroquel clinical trials with a $QTc \geq 450$ ms constituted “reasonable evidence of a causal association with”

Seroquel and QT/QTc prolongation; “a causal relationship need not have been definitively established.” By April 2004, AstraZeneca’s duty to change the Seroquel label adding a warning about the dangers posed by concomitant use of quetiapine with other QT/QTc prolonging medications was triggered yet again.

311. On June 16, 2004, the MEB report for Seroquel was issued. The document reported five reports of cardiac arrest, eleven reports of death “not otherwise specified,” six reports of sudden death, ten reports of QTc prolongation with “confounding factors,” such as “concomitant medications” or “medical history” and three deaths attributed to a drug-drug interaction between methadone (a known QT/QTc prolonging drug) and quetiapine.

312. Additionally, the MEB reported, “for patients with hepatic disease (diseases of the liver) the most frequently reported AE (adverse event) was Electrocardiogram QTc interval prolonged...” The report read in relevant part:

There were 8 reports for patients with a history of renal disease, and 22 reports for patients with a history of hepatic disease. No trend of AEs was identified for patients with renal diseases, however for patients with hepatic disease the most frequently reported AE was Electrocardiogram QTc interval prolonged, besides several hepatic function related events.

313. In this same MEB report, the Dutch followed up on its request from January 2003 and asked AstraZeneca again to add a warning to its European Seroquel labels for quetiapine and QT prolongation in overdose. The MEB report reads in relevant part:

During the current period, 18 reports of QT related AEs were received. Three of these reports involved drug overdose and one report described drug misuse. It seemed that ten other reports contained confounding factors as concomitant medications or medical history. Furthermore, the MAH cited a case report of which a QT-prolongation measured automatically, manual check suggested an artefact. The authors recommended a manual check of the QTc interval to verify the ECG printout.

Assessor's comment: The MAH has submitted also an analysis on cardiac safety on request of the PhVWP. Assessment of this document will be more thoroughly also for these QT related events. However, in the assessment report of the previous PSUR, the MAH was requested to include QT-prolongation in section 4.9 'Overdose' of the SPC, because of several overdose cases with QT-prolongation. No type II variation has been submitted for this issue.

314. On September 29, 2004, an AZ PSUR for Seroquel was issued. The document reported three cases of sudden death (all female). One of the three cases was a patient taking quetiapine, haloperidol, and levomeprozine (both known QTc prolonging drugs). Another of the three cases was a patient taking quetiapine with risperidone (a known QTc prolonging drug) who developed QTc prolongation prior to her death. The document also reported a case of a patient who experienced ventricular tachycardia while taking quetiapine and a patient who developed QTc prolongation while taking quetiapine and risperidone concomitantly.

315. AstraZeneca tracked reports of adverse events that were “listed” in the quetiapine CDS and reports of adverse events that were “unlisted” in the quetiapine CDS. The September 29, 2004 PSUR included reports of “Serious Unlisted (in the product’s labeling) Adverse Events” that included:

Table 3. Cumulative Tabulation of Serious Unlisted Adverse Events (Continued)

System Organ Class		
High Level Group Term	11-MAR-2004 to 31-JUL-2004	Total up to 31-JUL-2004
Preferred Term		
Electrocardiogram abnormal		3
Electrocardiogram change		2
Electrocardiogram PR prolongation		1
Electrocardiogram QRS complex prolonged		1
Electrocardiogram QT corrected interval prolonged	6	22
Electrocardiogram QT prolonged	3	32
Electrocardiogram R on T phenomenon		1
Electrocardiogram ST segment depression		1
Electrocardiogram T wave amplitude decreased		1
Electrocardiogram T wave inversion		2

316. Accordingly, from September 1997 through July 31, 2004, there were a total of 66 reports of abnormal electrocardiograms, including QT prolongation and QTc prolongation, associated with patients who had taken quetiapine.

317. The September 29, 2004 AZ PSUR also reported that the European Pharmacovigilance Working Party directed AZ to conduct a full review of AZ safety databases

to “examine the effect of SEROQUEL on cardiac safety, including QTc prolongation, Torsades de Pointes, and sudden death.”

318. In January 2005, a study in the Annals of General Psychiatry showed that when antipsychotics, including quetiapine, are used concomitantly with antidepressants the average increase in the QTc interval was 24 ms.

319. On October February 4, 2005, the Texas Department of Aging Services/Texas Department of State Health Services (“DADS/DSHS”) Executive Formulary Minutes indicated that a Texas Medicaid beneficiary experienced QTc prolongation after taking quetiapine with haloperidol and paroxetine:

A 23-year-old male was prescribed paroxetine (Paxil®) CR and quetiapine (Seroquel®), which the patient was receiving prior to admission. On admission, simvastatin (Zocor®) was started. A day after admission, the patient received two doses of haloperidol (Haldol®). The patient developed possible neuroleptic malignant syndrome with hypertension, tachycardia, increase CK (troponins were within normal limits), leukocytosis, QTc prolongation, and chest pain. The patient's lumbar puncture was normal.

320. On April 20, 2005, the MEB report for Seroquel was issued. The document reported one case of QTc prolongation was associated with the concomitant use of fluoxetine (an antidepressant) and quetiapine, nine cases of QTc prolongation at therapeutic doses with one of the patients experiencing ventricular tachycardia. Lastly, the MEB directed AZ to “closely monitor QTc prolongation and Torsades de Pointes.”

321. In this same MEB report, the Dutch followed up on its request from January 2003 (some twenty-eight months after its initial request) and asked AstraZeneca yet again to add a warning to its European Seroquel labels for quetiapine and QT prolongation in overdose. The MEB report reads in relevant part:

Assessor's comment: Several of these events are mentioned in the SPC in section 4.9. However, with other antipsychotic drugs mainly in overdose situations cardiac arrhythmias and QT prolongation is observed. The MAH should closely monitor these cardiac events following overdoses of quetiapine. Furthermore, as already requested QT prolongation should be included in section 4.9 of the SPC.

DISCUSSION

The previous PSUR assessment was part of the renewal procedure. During the renewal procedure, the SPC has been updated to include neonatal withdrawal symptoms in section 4.6 of the SPC, ADRs headache, tardive dyskinesia, and Stevens Johnson syndrome in section 4.8 of the SPC. Based on the PhVWP analysis of QT prolongation and QT prolongation should be included in section 4.9 of the SPC. A type II variation is ongoing.

322. Consequently, any argument AstraZeneca could make that any subsequent label change related to quetiapine and QT prolongation resulting in a “caution” warning being added to the quetiapine Core Data Sheet was based on “new” information related to quetiapine and QT prolongation would fail.

323. As the FDA itself has explained, “newly acquired information,” is not limited to new data, but also encompasses “new analyses of previously submitted data.” See *Wyeth v. Levine*, 555 U.S. 555, 565 (2009).

324. In May 2005, a study in the *European Heart Journal* reported that the risk of sudden cardiac death was **quintupled** by the use of haloperidol.

325. In June 2005, results from the Merck/Schering Study A7501001 (“Merck study”) showed that Seroquel caused increases in the QTc interval of **7.5 ms to 9.9 ms from placebo**.

326. The Merck study was a head to head study of Seroquel and asenapine (first known as “Sycrest” and then “Saphris”).

327. Furthermore, the results of this study showed “QTc prolongation and a small relationship between QTc and plasma drug concentrations (**a dose response relationship**).” The narrative from the June 16, 2009 MEB report concerning this study reads in relevant part:

During the period under review in the medical literature a 16-day multicentre double-blind study in which the effects of QTcF for asenapine versus quetiapine and placebo were investigated found a mean increase of 9.9 msec (from placebo) on day 16 for quetiapine 750 mg. The results showed QTc prolongation and a small relationship between QTc and plasma drug concentrations.

328. In May 15, 2008, FDA reviewers Ronald E. Kavanagh and Raman Baweja published their review of the Merck/Schering study. Their review reads in relevant part:

Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Team Leader:	Raman Baweja, Ph.D.

Figure 156 and Figure 158 shows the sponsor's linear models of $\Delta\Delta\text{QTcF}$ vs. plasma asenapine and quetiapine concentrations. It's clear that asenapine concentrations do go up to 20 ng/ml and that most concentrations between 10 and 20 ng/ml are achieved by a dose of 20 mg BID followed by a dose of 15 mg BID, although the mean and upper limits of the CI are much lower than the values seen with the post-administration time dose data. In addition, most Quetiapine concentrations are below 2000 ng/ml at a dose of 375 mg BID which is within the therapeutic dose range of 400 – 800 mg daily. Assuming the highest concentration seen with quetiapine is 2750 ng/ml the maximum dose may result in concentrations of nearly 6000 ng/ml in some individuals. This translates into a $\Delta\Delta\text{QTc}$ of over 35 mSec in spite of this quetiapine is not generally considered to have a higher than normal incidence for arrhythmic potential.

329. Consequently, on May 15, 2008, AstraZeneca was on notice that Seroquel could increase the QTc interval by 35 milliseconds and that increases in the QTc interval caused by Seroquel were dose-dependent.

330. On August 1, 2008, Dr. Thomas Laughren, Director Division of Psychiatry Products, completed his review of the asenapine ("Saphris") new drug application titled "Recommendation for approvable action for asenapine sublingual tablets for the acute treatment of schizophrenia and for the acute treatment of mania and mixed episodes of bipolar 1 disorder."

331. His review reads in relevant part:

QTc Increases

A thorough QT study for asenapine involving doses in a range of 5 mg bid to 20 mg bid revealed a small mean increase in QTc for asenapine of about 5-10 msec. There was not a clear dose response relationship for QT prolongation, however, the upper 95% confidence interval exceeded 10 msec for all 4 doses. Thus, this was a positive study. Quetiapine was an active control in this study and had a roughly comparable effect on QT prolongation. Asenapine should have the standard warning language for drugs with a modest QT prolonging effect, but would not be expected to be associated with Torsade des Pointes under ordinary circumstances of use.

332. Initial proposed label for asenapine read as follows:

14.3 Thorough QT/QTc Trial

A trial assessing the potential QT/QTc prolonging effect of Sycrste 5 mg, 10 mg, 15 mg, and 20 mg b.i.d. and placebo was conducted in 151 clinically stable patients with schizophrenia. Electrocardiographic assessments were performed throughout the dosing interval both at baseline and steady state. ~~The mean increase in QTc from baseline at C_{max}, as derived from exposure response analysis, was 1.9 ms, 3.0 ms, 3.7 ms, and 4.9 ms for Sycrste 5 mg, 10 mg, 15 mg, and 20 mg b.i.d., respectively; and 7.5 ms for quetiapine 375 mg b.i.d.~~ There was a concentration-dependent increase in QTc interval. ~~Categorical analyses for this study revealed that~~ No patients treated with Sycrste experienced QTc increases >60 ms from baseline measurements, nor did any patient experience a QTc of >500 ms. Additionally, there were no reports of Torsade de Pointes or any other adverse events associated with delayed ventricular repolarization.

333. After determining that asenapine (“Saphris”) and quetiapine “had a roughly comparable effect on QT prolongation”, the FDA required asenapine to have the following “should be avoided” warning related to QT prolongation on its label:

The use of SAPHRIS should be avoided in combination with other drugs known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin). SAPHRIS should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including bradycardia; hypokalemia or hypomagnesemia; and presence of congenital prolongation of the QT interval.

334. Dr. Laughren further stated “the prolongation of the QT interval appears to have vanishingly little clinical relevance in patients who are not co-administered drugs that prolong the QT interval.”

335. Despite the FDA’s Director Division of Psychiatry Product’s own conclusion that asenapine and quetiapine had a “roughly comparable effect on QT prolongation” and the identification of the clear risk of QT prolongation in patients who are co-administered drugs that

prolong the QT interval, the United States Seroquel label would not contain the comparable “should be avoided” warning until June 2011.

336. Importantly, the Supreme Court stated in Wyeth v. Levine that:

regulation. The FDA has limited resources to monitor the 11,000 drugs on the market,¹¹ and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.

337. The FDA’s decision to include the “should be avoided” warning on Saphris’ label constituted “reasonable evidence of a causal association with” Seroquel and QT/QTc prolongation and triggered AstraZeneca’s statutory duty to amend the Seroquel and Seroquel XR labels pursuant to the CBE regulation.

338. On September 22, 2005, the CATIE study was published in the New England Journal of Medicine. The CATIE study was a comparative study of olanzapine (Zyprexa), quetiapine, risperidone (Risperdal), perphenazine (a typical antipsychotic) and Ziprasidone (Geodon) and was funded by the National Institute of Mental Health.

339. Importantly, the CATIE study excluded patients with known QTc prolongation and patients taking medications known to increase the QTc interval:

11. Patients with the following cardiac conditions are excluded:

- Recent myocardial infarction (<6 months)
- QTc prolongation (screening electrocardiogram with QTc > 450 msec for men, QTc > 470 msec for women)
- History of congenital QTc prolongation
- Sustained cardiac arrhythmia or history of sustained cardiac arrhythmia
- Uncompensated congestive heart failure
- Complete left bundle branch block
- First-degree heart block with PR interval ≥ 0.22 seconds

12. Patients on concurrent treatment with dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus are excluded.

340. Despite the fact that these patients were excluded, the CATIE results nevertheless showed that 3% of the cohort of quetiapine patients with an average age of 40 and 6% in the

cohort of quetiapine patients with dementia with an average age of 78 **developed clinically significant QTc prolongation.**

341. Furthermore, in the CATIE study the average effect of quetiapine on the QTc interval was **19 ms.** Of all the antipsychotics studied in the CATIE trial – olanzapine, perphenazine, risperidone, ziprasidone and quetiapine – **only quetiapine** had a statistically significant effect on the QTc interval.

342. In October 2005, the FDA issued a statement that the “threshold of regulatory concern (for QTc prolongation)...is about 5 ms (milliseconds)...”

343. On November 17, 2005, the results of Seroquel Study 135 were published internally at AstraZeneca. The study found that 2.4% of patients in the 300 mg arm of the study experienced “shifts to high” in their QTc interval compared to 1.4% for placebo. AZ’s definition of “shift to high” was any change ≥ 60 ms whereas the clinical standard was ≥ 30 ms. This change in definition presumably skewed the results of the study in Seroquel’s favor. Additionally, one patient in the Seroquel arm of the study experienced QTc prolongation in excess of 500 ms.

344. On an unspecified date in 2006, a MEB report for Seroquel was issued. The document reported 20 cases of QTc prolongation with quetiapine and 11 cases of sudden death during the covered time period.

345. On an unspecified date in 2006, the AZ Corporate Responsibility Report was published wherein AZ pledged that if “information suggests a change is needed in a benefit/risk profile (for a drug), the actions we [AZ] can take include **conducting further clinical trials, modifying the prescribing information, and communicating with healthcare professionals and others who need to know of the change.**”

346. On January 17, 2006, the study titled “Prolonged QTc Interval and Risk of Sudden Cardiac Death in a Population of Older Adults” was published in the *Journal of the American College of Cardiology*. The study found that abnormally prolonged QTc intervals (>450 ms in men, >470 in women) was associated with a **three-fold increased risk of sudden cardiac death**, after adjustment for age, gender, body mass index, hypertension, cholesterol/high-density lipoprotein ratio, diabetes mellitus, myocardial infarction, heart failure, and heart rate. Additionally, the study also found that in patients below the age of 68 years, an abnormally prolonged QTc interval was associated with an **eight-fold increased risk of sudden cardiac death**.

347. In February 2006, the European Union Pharmacovigilance Working Party required manufacturers of all antipsychotics, including AstraZeneca, to include a warning in their drugs’ labels (including quetiapine) about the drugs’ effects on QTc prolongation to advise **caution when antipsychotics are used concomitantly with other drugs known in to increase the QTc interval**.

348. As of February 2006, the European Union determined that there was “intermediate” evidence of an association between quetiapine and QTc prolongation.

349. Additionally, the additional warning language for QT prolongation in quetiapine overdose that the MEB requested over three years earlier was added:

Upon the request from the MEB on 12 February 2006, the wording “In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. However, with overdose QT prolongation was observed. As with other antipsychosis, caution should be exercised when quetiapine is prescribed with medicines known to increase QT interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia” was added.

Prolonged QT/Torsade de Pointes

During the covered period 25 related reports were received, five were reported as QT prolongation following an overdose, the rest of 20 reports lacked baseline QT values. Four cases were recorded with confounded diseases and the rest of the cases had scant medical information, giving the difficulty for assessing the casual relationship. A review of all controlled clinical trials showed that the incidence density for quetiapine was not higher than that for placebo. The MAH concluded no changes for CDS is warranted for this time.

Assessor's comment: The MAH should be aware of a conclusion of the Jan 2006 from PhvWP in which quetiapine was classified in the group with potential risk. The proposal for amending the SPC according has been sent to the MAH.






350. In July 2006, a study was published in the *British Journal of Clinical Psychopharmacology* that showed that taking more than one QTc prolonging drug at the same time nearly quintupled the risk of cardiac arrest.

351. On September 20, 2006, the AZ PSUR for Seroquel was issued. The document reported twenty cases of QTc prolongation. Three of the twenty reports were patients taking fluoxetine (Prozac), venlafaxine (Effexor) and ziprasidone (Geodon) concomitantly with quetiapine. All three drugs are associated with increases in the QTc interval.

352. Also in September 2006, the American College of Cardiology/American Heart Association/European Society of Cardiology published the *2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death* ("the Guidelines"). In the Guidelines, haloperidol is classified as a "well known" drug that causes "marked QTc prolongation and torsades de pointes."

353. The Guidelines also listed the "Risk Factors for Drug-Induced Torsades de Pointes:

Table 10. Risk Factors for Drug-Induced Torsades de Pointes

-
- Female gender 
 - Hypokalemia 
 - Bradycardia 
 - Recent conversion from atrial fibrillation
 - Congestive heart failure 
 - Digitalis therapy
 - High drug concentrations (*exception: quinidine*), often due to drug interactions
 - Rapid rate of intravenous drug administration
 - Baseline QT prolongation
 - Ventricular arrhythmia
 - Left ventricular hypertrophy
 - Congenital long QT syndrome
 - Certain DNA polymorphisms
 - Severe hypomagnesemia 
 - Concomitant use of 2 or more drugs that prolong the QT interval
 - Combination of QT-prolonging drug with its metabolic inhibitor
-

354. On December 4, 2006, the results from a comparative study between paliperidone and quetiapine are released showing that quetiapine increased the QTc interval versus placebo 5.4 to 8.1 ms (the “Janssen study”).

355. The Janssen study reached the following conclusion about the relative impact of quetiapine on the QTc interval relative to paliperidone:

SUMMARY – CONCLUSIONS

PHARMACODYNAMIC RESULTS: The primary comparison of interest was the change from baseline in QTcLD between once daily paliperidone ER 12 mg and quetiapine 400 mg twice daily at individual’s observed t_{max} on Days 6-7 (steady state). At steady state the least squares mean change from baseline in QTcLD at each individual’s observed t_{max} was 1.1 ms for paliperidone ER 12 mg and 6.1 ms for quetiapine. Given that the mean difference in QTcLD between paliperidone ER 12 mg and quetiapine was estimated to be 5.1 ms lower for paliperidone ER 12 mg with the upper limit of the 2-sided 90% CI [-9.2, -0.9] not exceeding 10 ms, noninferiority of once daily paliperidone ER 12 mg compared to quetiapine 400 mg twice daily is concluded.

A similar comparison was performed between a supratherapeutic dose of paliperidone ER (18 mg) and quetiapine 400 mg twice daily. At steady state, the mean change from baseline in QTcLD at individual’s observed t_{max} was 3.7 ms for paliperidone ER 18 mg and 6.0 ms for quetiapine, and the mean difference in QTcLD between paliperidone ER 18 mg and quetiapine was estimated to be 2.3 ms lower (90% CI [-6.8, 2.3]) for paliperidone ER 18 mg. The upper limit of the 2-sided 90% confidence interval was <10 ms.

356. Consequently, two separate end points of the study established that quetiapine caused a greater increase in the QTc interval than paliperidone.

357. On December 19, 2006, Dr. Mitchell Mathis from the FDA submitted his report on paliperidone titled "Recommendation of Approval Action for Paliperidone Extended Release OROS Oral Tablets for the Treatment of Schizophrenia."

358. Dr. Mathis' report on paliperidone's effect on the QTc interval reads in relevant part:

5.2.1 QT Prolongation

Although there is no signal from the phase 3 trials, paliperidone ER has a modest QT effect as judged from the sponsor's thorough QT study (SCH-1009). We consulted the Division of Cardiorrenal Products (DCRP) for assistance in interpreting the results of this study and verification of corrected QT interval calculations from ECGs submitted to FDA's ECG warehouse. DCRP suggested language for the QT Prolongation section of labeling and recommended this language be included under Warnings because of the identified moderate risk (Pbo-subtracted QTcLD increase from baseline = 12.3 msec). We agree with this recommendation and have included this language under the Warnings section of labeling. The sponsor suggested that language describing

359. On January 3, 2007, paliperidone was launched in the United States with the following warning about QTc prolongation:

QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

360. Despite the fact that quetiapine had a greater impact on the QTc interval than paliperidone, the quetiapine label would not have a comparable warning in its label until June 2011.

361. Under federal law, it was incumbent on AstraZeneca to change the Seroquel label to include new warnings about QT/QTc “as soon as there [was] reasonable evidence of a causal association with” Seroquel and QT/QTc prolongation; “a causal relationship need not have been definitively established.”

362. The FDA’s decision to include the “should be avoided” warning on paliperidone’s label constituted “reasonable evidence of a causal association with” Seroquel and QT/QTc prolongation and triggered AstraZeneca’s statutory duty to amend the Seroquel and Seroquel XR labels pursuant to the CBE regulation.

363. By December 2006, the results of at least six studies – AZ Study 0013, AZ Study 0015, Pfizer Study 054, the Janssen study, the CATIE study and Merck/Schering Study A7501001 – had shown that quetiapine caused clinically and statistically significant increases in the QTc interval at **therapeutic** doses.

364. AZ Study 0013 showed an increase from baseline to endpoint of 10 milliseconds in the 600 mg group and this change was statistically significant in comparison to **placebo**. AZ has known the results of this study since at least 1997.

365. In AZ Study 0015, four patients had “treatment emergent QTc greater than 500 ms compared to one each in the 300 and 75 mg groups and **none in the haloperidol group**.” AZ has known the results of this study since at least 1997.

366. In fact, in internal AZ communications AZ employee Richard Lawrence referred to Study 0015 as a “cursed study” because of the negative results for quetiapine.

367. Pfizer Study 054 (“Study 054”) was a study conducted to measure the effect of Geodon, Risperdal, Zyprexa, Seroquel, Haldol, and Mellaril on the QTc interval. AZ has known the results of this study since at least July 2000.

368. In Study 054, 52% of Seroquel patients showed increases in QTc prolongation of greater than 30 milliseconds and 11% of Seroquel patients showed increases greater than 60 milliseconds. Study 054 was subsequently published in the *Journal of Clinical Psychopharmacology* in 2004.

369. Interestingly, the *Journal of Clinical Psychopharmacology* was the same journal where the Uehlinger study was published.

370. On January 9, 2007, or over three years before AstraZeneca initiated its “Changes Being Effected” regulation label change advising “caution” when Seroquel was used with other QT/QTc prolonging medications, a New York State Medicaid beneficiary (“Doe”) was rushed to the hospital complaining of shortness of breath and chest pain.

371. Shortness of breath and chest pain are symptoms associated with clinically significant QT/QTc prolongation.

372. Doe had three separate ECGs performed. Each showed the result “Prolonged QT” and “Abnormal ECG.”

373. Doe was on four separate medications: methadone, paroxetine, Lasix, and Seroquel.

374. In May 2007, the United States label for Haldol was amended pursuant to the Changes Being Effected regulation to include new warnings for QTc prolongation. The warning read in relevant part:

WARNINGS

Cardiovascular Effects

Cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including HALDOL.

Since QT-prolongation has been observed during HALDOL treatment, it is advised to be cautious in patients with QT-prolonging conditions (long QT-syndromes, hypokalaemia, electrolyte imbalance, drugs known to prolong QT, cardiovascular

diseases, family history of QT prolongation). HALDOL INJECTION IS NOT APPROVED FOR INTRAVENOUS ADMINISTRATION.

375. Janssen changed both the labels for both the oral and intramuscular versions of haloperidol. The oral version of haloperidol was changed to include the following warning:

WARNINGS

Cardiovascular Effects

Cases of sudden death, QT-prolongation, and Torsades de Pointes have been reported in patients receiving haloperidol. Higher than recommended doses of any formulation of haloperidol appear to be associated with a higher risk of QT-prolongation and Torsades de Pointes. Although cases have been reported even in the absence of predisposing factors, particular caution is advised in treating patients with other QT-prolonging conditions (including electrolyte imbalance [particularly hypokalemia and hypomagnesemia], drugs known to prolong QT, underlying cardiac abnormalities, hypothyroidism, and familial long QT-syndrome).

376. On September 17, 2007, the FDA issued a "Safety Alert" to physicians concerning the effect of Haldol on the QT/QTc interval.

377. Furthermore, on that same date AstraZeneca misrepresented the results of Study 054 stating in relevant part its Periodic Safety Update Report stating in relevant part:

AstraZeneca also considers the prospective, comparative study performed by Pfizer (study 54) and designed with FDA input. This well controlled study specifically designed to evaluate QT intervals with a direct safety comparison of ziprasidone with haloperidol, thioridazine, olanzapine, risperidone, and quetiapine (Harrigan et al 2004) was designed to record ECGs at the estimated Tmax for each drug. The trial also included a phase in which a metabolic inhibitor was added to each of these drugs to determine the additive effects on the QTc interval of the expected maximal inhibition of the clearance of each drug.

Study 054 did not include a placebo-treated group. However, for the purposes of this trial, haloperidol was considered a placebo because of the "...abundance of data from multiple independent development programs showing no difference between haloperidol (at the oral dose used in study 054) and placebo on QTc." (Laughren 2000)

The effects of quetiapine were studied over a range of individual plasma concentrations that varied by 2 orders of magnitude, from approximately 102 ng/mL to approximately 104 ng/mL (Gordon 2000). All the correction formulae applied to the data, with the exception of the Bazett formula (known to overestimate the QTc interval when the heart rate is increased), confirmed that the change in QTc interval during quetiapine treatment was no greater than the change during haloperidol treatment.

Taken together, following a review of all data, it was determined that no changes to the CDS or other actions are warranted at this time regarding SEROQUEL/SEROQUEL XR and QT prolongation or Torsade de Pointes.

378. First, although AZ points out that the study showed "that the change in QTc interval during quetiapine treatment was no greater than the change during haloperidol treatment," AZ failed to reference the fact that the **haloperidol label had a specific warning about QTc prolongation** and that haloperidol was in fact subject to an FDA Safety Alert related to QTc prolongation **on the same day the AZ Seroquel PSUR was submitted to the FDA**. The FDA approved both the label change and the Safety Alert.

379. Additionally, **since at least April 2000**, haloperidol was classified by as a drug associated with QTc prolongation and Torsades de Pointes.

380. Third, the September 17, 2007 PSUR failed to mention either the **results of the Merck study or the Janssen study** let alone the fact that both the Merck and Janssen studies used the **Frederica standard** (AstraZeneca's preferred correction method) to monitor the drugs' relative effects on the QTc interval.

381. Furthermore, in Study 0015, **six** quetiapine patients experienced treatment emergent QTc greater than 500 ms whereas no Haldol patients did.

382. The September 17, 2007 PSUR also contained a report of a patient who experienced QT segment elongation (QT prolongation), cardiac arrest, and Torsades de Pointes while taking methadone with quetiapine. The report reads in its entirety:

The second report (██████████): "Drug interaction", Torsade de pointes", "Cardiac arrest", "Electrocardiogram QT prolonged", "Blood electrolytes abnormal", "Hypothyroidism") described a ██████████ patient who developed QT segment elongation, Torsade de Pointes, and cardiac arrest. During the hospitalization, ████████ electrolytes were abnormal (not otherwise specified) and hypothyroidism was diagnosed. Concomitant medications included metoprolol, hydroxyzine, alprazolam, ramipril, and magnesium citrate. SEROQUEL was discontinued and the outcome was not reported. This report provided

PSUR
Drug Substance Quetiapine fumarate
Date 17 September 2007

limited information for assessment of causality; no laboratory data was provided. The events of QT prolongation and Torsade de Pointes have been reported with methadone use alone and therefore could have occurred in the absence of a drug interaction with SEROQUEL. The patient's abnormal electrolytes may also have been a confounding factor.

383. The September 17, 2007 PSUR contained another report of a patient who was diagnosed with Post Traumatic Stress Disorder ("PTSD") who died with both methadone and quetiapine present. That report reads in its entirety:

PSUR Appendix G
Drug Substance Quetiapine fumarate
Date 17 September 2007

Table 26 Reports of death cause unknown without autopsy (patients 19 to 64 years of age)

Report #	Age/Sex	Dose/TTO	Concomitant meds	Medical history	Comments
██████████ Death	██████	Unk; 2 mos	Fluoxetine, vicodin, carisoprodol, hydrocodone, methadone	Scoliosis, PTSD	Pt taking painkillers for injuries due to boat accident. Two months after beginning tx with Seroquel pt died, no further info provided. AZ comment: Case confounded by con meds (methadone and fluoxetine for which QT prolongation and torsades de pointes has been reported). Limited information for analysis.

384. Consequently, AZ readily states that QT prolongation and torsades de pointes have been reported for fluoxetine and methadone, yet failed to do so for quetiapine.

385. The September 17, 2007 PSUR also included a separate report of QTc prolongation in a patient aged 2 to 11 years.

386. The September 17, 2007 PSUR also included notification that the European Union had required AstraZeneca, and all other atypical antipsychotic manufacturers, to include a warning related to QT prolongation:

Update of Regulatory Authority or Marketing Authorization Holder actions taken for safety reasons

The European Union (EU) Pharmacovigilance Working Party (PhVWP) had requested manufacturers of all atypical antipsychotic agents to include information in the labeling regarding QT prolongation. AstraZeneca received notification from the MEB regarding this request on 12 February 2006 and final updates to the SmPC have been completed during this reporting period.

387. The United States label for Seroquel, which Drug Utilization Review Boards materially relied upon, did not include any warning related to the dangers of the concomitant use of quetiapine and other drugs known to cause increases in the QT/QTc interval until January 2010.

388. The September 17, 2007 PSUR also included a narrative of a patient between the ages of 19 and 64 who died while taking Seroquel with three other drugs – risperidone (Risperdal), venlafaxine (Effexor), and escitalopram (Lexapro) – known definitively at the time to cause QTc prolongation:

PSUR Appendix G
Drug Substance Quetiapine fumarate
Date 17 September 2007

Table 26 Reports of death cause unknown without autopsy (patients 19 to 64 years of age)

Report #	Age/Sex	Dose/TTO	Concomitant meds	Medical history	Comments
Death		≤400 mg/day; duration unk	Venlafaxine, oxcarbazepine, escitalopram, risperidone*	Sleep apnea, depression	Pt's dose of Seroquel was ↑ to 400 mg at bedtime the night died. No other info. AZ comment: Case confounded by both med Hx (sleep apnea syndrome) & con meds (risperidone, for which QTc prolongation resulting in death has been reported).

389. The September 17, 2007 PSUR also included a narrative of patient (with “mental retardation (severity unspecified)”) between the ages of 19 and 64 who died while taking Seroquel with Effexor:

PSUR Appendix G
Drug Substance Quetiapine fumarate
Date 17 September 2007

Table 26 Reports of death cause unknown without autopsy (patients 19 to 64 years of age)

Report #	Age/Sex	Dose/TTO	Concomitant meds	Medical history	Comments
Death		200-600 mg/day; ≈4 mos	Valproate, venlafaxine, lansoprazole	Mental retardation (severity unspecified)	Pt died after taking Seroquel for ≈4 mos. No other info. AZ comment: Report contained scant clinical detail.

390. Importantly, AstraZeneca directed and incentivized its representatives to promote Seroquel for use in patients with mental retardation.

391. On October 12, 2007, Texas DADS/DSHS Executive Formulary Minutes indicate QTc prolongation occurred after the initiation of quetiapine:

A 40 year old female was admitted to a state hospital for the treatment of schizoaffective disorder. She was initially prescribed ziprasidone (Geodon®) 120 mg/day and duloxetine (Cymbalta®) 60 mg/day. The ziprasidone dose was increased to 160 mg/day and quetiapine (Seroquel®) was initiated and increased to 300 mg/day. Trazodone (Desyrel®) 100 mg was added at bedtime. An EKG was obtained eleven days after admission and it showed QTc prolongation of 477 msec (QT interval 386 msec). No other cardiac abnormalities were noted. The patient did not complain of syncope, palpitations, or other cardiovascular symptoms during her hospital stay. The patient did not have any history of cardiac conduction abnormalities. No baseline or follow-up EKGs were obtained. The ziprasidone was tapered and discontinued during this hospitalization.

392. In June 2008, the MEB strongly rebuked AZ for its interpretation of Study 054.

The MEB's review of the QT safety information pertaining to quetiapine reads in its entirety:

Prolonged QT/Torsade de Pointes

During the period under review 27 reports were retrieved using the MedDRA SMO Torsade de Pointes/QT prolongation tool of which 16 were serious and 11 non-serious:

- ECG QTc interval (1 report, serious)
- ECG QTc interval prolonged (9, 5 serious, 4 non-serious)
- ECG QT interval abnormal (1, serious)

- ECG QT prolonged (15, 8 serious, 7 non-serious)
- Torsade de Pointes (4, serious).

Three reports contained both terms ECG QT prolonged and Torsade de Pointes.

One of the 27 reports (coded as ECG QTc interval prolonged) had a fatal outcome. The case was however poorly documented. Another four reports described QT prolongation following an overdose, which is listed.

Three other cases had a positive quetiapine dechallenge. In two other cases the prolonged QT interval led to quetiapine discontinuation. The remaining cases were either confounded by concomitant medication (for instance ziprasidone, olanzapine) or concurrent illness/ medical history, did not have a temporal relationship with quetiapine, or contained limited information.

The MAH also considered the 2004 prospective comparative study performed by Pfizer and designed with FDA input to evaluate QT intervals with a direct safety comparison of ziprasidone with haloperidol, thioridazine, olanzapine, risperidone and quetiapine. The change in QTc interval during quetiapine treatment was no greater than the change during haloperidol treatment, which was considered the 'placebo'.

Assessor's comment: The SPC was recently updated after the conclusions from the PhVWP in Jan 2006 in which quetiapine was classified in the group with potential risk for QTc prolongation, cardiac arrhythmia, tachycardia and torsade de pointes. It should be noted that haloperidol was classified in the group of established risk, which disputes the use of haloperidol as a 'placebo' and consequently the results of the 2004 study mentioned by the MAH.

393. In sum, the MEB reported that the European Union's Pharmacovigilance Working Party concluded in January 2006 that quetiapine was classified as having potential risk for QTc prolongation, cardiac arrhythmia, tachycardia (rapid heartbeat), and torsades de pointes whereas haloperidol was classified as having an established risk for QTc prolongation, cardiac arrhythmia, tachycardia (rapid heartbeat), and torsades de pointes.

394. According to the MEB, this determination effectively discredited AstraZeneca's use of "haloperidol as a 'placebo' and consequently the results of the study mentioned by the MAH (Market Authorization Holder – AstraZeneca)."

395. Consequently, in its September 2007 PSUR, AZ failed to disclose the following highly relevant facts about haloperidol's relative effect on the QT/QTc interval vis-à-vis quetiapine:

1. The fact that in Study 0015 six patients in the quetiapine arm and no patients in the haloperidol arm had treatment emergent QTc measurements of 500 ms or greater;
2. The fact that as of May 2007 (or earlier) the haloperidol label in the United States and Europe had a specific warning concerning its effect on the QTc interval;

3. The fact that haloperidol was subject to an FDA Safety Alert on the same day as the September 17, 2007 AZ Seroquel PSUR;
4. The fact that in February 2006 the European Union had placed haloperidol in the group of drugs that have an “established risk” for prolonging the QT interval; and
5. The fact that haloperidol had been long classified as a drug that causes QTc prolongation and was associated with Torsades de Pointes.

396. Despite the MEB’s June 2008 admonition, AZ nevertheless used substantially the same reasoning, *and left out the same facts relative to haloperidol*, in its March 13, 2009 briefing document submitted to obtain market authorization for Seroquel XR to the FDA:

Advisory Committee Briefing Document
Drug Substance: quetiapine fumarate extended release (XR)
Date: 13 March 2009

In this prospective, comparative study performed by Pfizer and designed with FDA input, the effects of quetiapine were studied over a range of individual plasma concentrations that varied by 2 orders of magnitude, from approximately 10^2 ng/mL to approximately 10^4 ng/mL (Gordon 2000). All the correction formulas applied to the data, with the exception of the Bazett formula (known to overestimate the QTc interval when the heart rate is increased), confirmed that the change in QTc interval during quetiapine treatment was no greater than the change during haloperidol treatment.

397. This verbiage amounts to simply a regurgitation of the same analysis that was fully discredited by the MEB.

398. The March 2009 Seroquel XR briefing document also stated:

The cardiovascular toxicity of the older generation of tricyclic antidepressants is well established (American Psychiatric Association 2000, Pacher and Kecskemeti 2004). In addition, an increasing number of case reports have demonstrated that the use of SSRIs is associated with cases of arrhythmias, prolonged QTc interval and orthostatic hypotension in patients lacking cardiovascular disorder (Pacher and Kecskemeti 2004).

399. Seroquel XR is indicated as adjunct therapy alongside certain antidepressants for major depressive disorder.

400. Seroquel XR was studied alongside the antidepressants venlafaxine (“Effexor”), citalopram (“Celexa”), escitalopram (“Lexapro”), and amitriptyline (“Elavil”) for its adjunct depression indication.

401. Venlafaxine (“Effexor”), citalopram (“Celexa”), escitalopram (“Lexapro”) and amitriptyline (“Elavil”) are all associated with QTc prolongation.

402. The use of Celexa and Lexapro are **contraindicated** with quetiapine in the United Kingdom because of the risks of QTc prolongation posed by the concomitant usage of these either Celexa or Lexapro with quetiapine.

403. State Medicaid agencies often employ third parties (that form the basis of the Compendia) to inform them of the dangers posed by drug interactions. One of the vendors used by the State of Texas, and Medicaid plans nationwide, is *Clinical Pharmacology*.

404. The Clinical Pharmacology drug interaction report for quetiapine and citalopram currently reads in relevant part:

Drug to Drug Interactions

Citalopram and Quetiapine

Concurrent use of quetiapine and citalopram should be avoided if possible. Citalopram causes dose-dependent QT interval prolongation and quetiapine is associated with a possible risk for QT prolongation and torsade de pointes (TdP).^[28269] ^[29118] According to the manufacturer of citalopram, ECG monitoring is recommended in patients receiving concurrent drugs that prolong the QT interval.^[28269] Because of the potential risk and

405. The *Clinical Pharmacology* drug interaction report for quetiapine and venlafaxine currently reads in relevant part:

syndrome. Finally, concurrent use of quetiapine with other drugs having a possible risk for QT prolongation and TdP such as venlafaxine ^[10568] should be avoided if possible.

406. Furthermore, in a study published in September 2011 in *Clinical Cardiology*, three patients (out of the eleven reviewed) developed TdP while taking quetiapine with escitalopram or citalopram:

Acquired Long QT Interval: A Case Series of Multifactorial QT Prolongation

Table 1. Patient Characteristics by Case

Case	1	2	3	4	5	6	7	8	9	10	11
Sex	F	F	F	M	F	F	M	F	F	F	M
Age (yr)	64	58	52	53	61	19	33	67	77	34	23
QTc (ms)	466	720	549	521	840	600	638	610	529	718	581
TdP	(+)	(+)	(+)	(+)	(+)	(-)	(-)	(+)	(+)	(+)	(-)
K ⁺ (mmol/L) ^a	2.9	2.5	3.3	2.4	2.8	3.1	2.8	2.7	3.4	2.6	2.5
Mg ²⁺ (mmol/L) ^b	0.62	0.75	0.90	0.74	0.85	0.85	0.70	0.61	0.71	0.80	0.77
QT-prolonging medications (direct and indirect)	Domperidone, venlafaxine, furosemide, metolazone	Citalopram, quetiapine, HCTZ	Fluvoxamine, HCTZ	Methadone, citalopram, HCTZ	Maxifloxacin, HCTZ, furosemide	Ciprofloxacin, domperidone, metronidazole	Domperidone	Escitalopram, quetiapine, furosemide	Citalopram, quetiapine, metronidazole, furosemide	Domperidone, furosemide	Maxifloxacin, azithromycin

407. Importantly, none of the three patients who had taken quetiapine experienced TdP in the aforementioned study had a reported or confirmed overdose of any of the drugs they ingested.

408. According to a March 2009 study published in the *British Journal of Clinical Psychopharmacology* titled “Clinically relevant QTc prolongation due to overridden drug-drug interaction alerts: a retrospective cohort study,” “31% of patients who received more than one QTc prolonging drug showed clinically relevant QTc prolongation with increased risk of torsades de pointes or ventricular arrhythmias.” The average change in QTc interval was +31 ms for cases and -4 ms for controls. Of the patients who experienced showed “clinically relevant QTc prolongation with an increased risk of torsades de pointes or ventricular arrhythmias,” 52% were receiving haloperidol, the same drug AZ has repeatedly stated, despite an FDA Safety Alert, label changes and a rebuke from the MEB, has a “placebo” like effect on the QTc interval.

409. On March 27, 2009, DADS/DSHS Executive Committee Meeting Minutes indicated a positive dechallenge for quetiapine and a “markedly prolonged” QTc interval occurred in a Texas Medicaid beneficiary on October 14, 2008:

A 43 year old female was admitted to a State Hospital on 10/10/08. The patient was suspected of probable noncompliance with her medications prior to admission. An EKG on 10/10/08 showed a normal QTc interval of 437 msec. All of her medications were restarted on 10/10/08, including quetiapine (Seroquel®) and cyclobenzaprine (Flexeril®). The EKG on 10/14/08 showed a QTc interval of 504 msec, which is markedly prolonged. The quetiapine was discontinued on 10/17/08. A repeat EKG obtained on 10/20/08 showed a QTc interval of 418 msec.

410. **On April 1, 2009**, AstraZeneca unilaterally amended its Core Data Sheet (also known as the “Company Core Data Sheet” or “CCDS”) to include the following information related to QT prolongation. AZ’s Periodic Safety Update Report stated:

The following text was amended in the “QT Prolongation” subsection of the SEROQUEL and SEROQUEL XR CDSs (dated April 2009):

QT Prolongation

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose (See section 4.9 Overdose). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e., the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesemia (See section 4.5 Interaction with other medicinal products and other forms of interaction).

411. In Dutch regulatory documents, the MEB refers to AstraZeneca as the Marketing Authorization Holder (“MAH”) for quetiapine (Seroquel and/or Seroquel XR).

412. The June 16, 2009 MEB report indicated that the Core Data Sheet was amended after a meeting of AstraZeneca’s “safety and evaluation review meeting” on **April 1, 2009**. As the MAH, AstraZeneca stated:

Second response MAH: QT prolongation was identified as a subject for review by the company internally and has been evaluated in the 01 April 2009 safety evaluation and review meeting. As a result the CCDS will be amended. Hereafter variations will be submitted to update the SPC.

Assessor's comment: Agreed.

413. Thus, as of April 1, 2009, when AstraZeneca changed the Core Data Sheet it determined that a warning advising caution when quetiapine is used concomitantly with other QT/QTc prolonging medications “**must be included** in every label around the world.”

414. The FDA itself has stated that a “new contraindications or warning...should be immediately conveyed to the user.” 50 FR 7452-01 (February 22, 1985) reads in relevant part:

Drug labeling serves as the standard under which FDA determines whether a product is safe and effective. Substantive changes in labeling * * * are more likely than other changes to affect the agency's previous conclusions about the safety and effectiveness of the drug. Thus, they are appropriately approved by FDA in advance, unless they relate to important safety information, like a new contraindication or warning, that should be immediately conveyed to the user.

(50 FR 7452-01, 7470, February 22, 1985).

415. On January 15, 2010, or some eight and a half months after the April 1, 2009 SERM meeting that added a warning advising “caution” when quetiapine is used with QT/QTc prolonging medications, AZ changed the Seroquel labels (Seroquel and Seroquel XR) pursuant to the “Changes Being Effected” regulation.

416. This new warning was distinct from the warning contained in the quetiapine labels prior to January 15, 2010 that advised “caution” when quetiapine was used with other “centrally acting agents” for two reasons. First, the new warning related to a **specific cardiac**

risk posed by the concomitant usage of quetiapine with QT/QTc prolonging medications. Secondly, most QT/QTc prolonging medications are not “centrally acting agents.”

417. Since February 2006, the labels for Seroquel in the European Union had advised “caution” when quetiapine is used concomitantly with QT/QTc prolonging medications.

418. Since July 1997, the labels for Seroquel in the United Kingdom had advised “caution” when quetiapine is used concomitantly with QT/QTc prolonging medications.

419. Since at least May 2008, the labels for Seroquel in Australia advised that “precautions” be taken when Seroquel was taken with QT/QTc prolonging medications.

420. On April 3, 2009, FDA documents that expressed concern about “possible risk of sudden cardiac death with atypical antipsychotic drugs – including quetiapine” were published online. In response, AstraZeneca’s stock dropped 3.9% and lost over \$1 billion in market capitalization.

421. The labels for Seroquel in the United States were silent on the dangers posed by quetiapine when it is used with QT/QTc prolonging medications until January 15, 2010, or some eight and half months after AstraZeneca concluded that the warning “must be included in every label around the world.”

422. C.F.R. 201.57 requires that “labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established.” (emphasis added).

423. Despite the fact that AstraZeneca determined on April 1, 2009 that there was “reasonable evidence” of the “clinically significant hazard” of quetiapine and QT/QTc prolongation, AstraZeneca did not change Seroquel’s label in the United States to include the warning that “caution” should be exercised when quetiapine is used with other medicines known

to increase QT/QTc interval until January 2010 by using the “Changes Being Effected” regulation.

424. Importantly, AstraZeneca itself defines that “Core Data Sheet” as a “summary of the company’s position with respect to essential scientific information, recommendations, and instructions needed for the safe and effective use of the product.”

425. AstraZeneca’s Dr. Martin Brecher testified under oath that once the Core Data Sheet was amended to add the warning about the use of quetiapine with other QT/QTc prolonging medications that warning had to “be included in every label around the world.”

426. Furthermore, AstraZeneca did not inform the FDA of this label change until January 2010 (or over eight and half months).

427. Thus, from April 1, 2009 through January 15, 2010, AstraZeneca withheld from the FDA, FDA Advisory Committees, physicians, pharmacists, State Drug Utilization Review Boards and State Pharmacy and Therapeutic Boards what it defined as “the essential scientific information, recommendations, and instructions needed for the safe and effective use of the product” related to Seroquel/Seroquel XR and QT prolongation.

428. Importantly, AstraZeneca has a history of changing its Seroquel label pursuant to the CBE regulation in a period of just two weeks.

429. In a filing with the FDA dated November 3, 2008, AstraZeneca explained that “[w]hen ever safety signals are identified they are further discussed and evaluated during AstraZeneca’s Safety Evaluation and Review Meeting (SERM) process, which leads to appropriate safety conclusions and actions (eg label changes) on the reviewed safety data.”

430. Thus, AstraZeneca itself identified “safety signals” related to quetiapine and QT/QTc prolongation before its April 1, 2009 QT/QTc SERM meeting and before the April 8, 2009 FDA Advisory Committee meeting.

431. Dr. Martin Brecher testified in his May 2008 deposition that “the critical point” in whether SERM changes the Core Data Sheet is “whether the label accurately reflects the safety profile as we [AstraZeneca] understand it.”

432. In Court filings on March 23, 2009, in a separate Seroquel case (or some eight days prior to the April 1, 2009 SERM meeting), AstraZeneca stated that it changed its Seroquel label “within two weeks” after convening a SERM meeting pursuant to the Changes Being Effected regulation stating in relevant part:

49; *see id.* at 59-62, 1037-38 (discussing analyses). The company then held a Safety Evaluation and Review Meeting (“SERM”) on June 8, 2007, to evaluate comprehensively glucose risks associated with Seroquel. *See* Deposition of Ronald Leong, M.D. (Ex. 12) at 251; *see also* Brecher Dep. (Ex. 9) at 1038-39. A week later, AstraZeneca finalized its core data sheet, concluding that the exposure adjusted rate of increased blood glucose (≥ 126 mg/dl) was 18.03 per 100 patient years taking Seroquel (10.7%) versus 9.53 for placebo. *See* AstraZeneca, *Clinical Overview: Glucose Dysregulation in Patients Treated With Seroquel* (June 2007) (Ex. 13) at 16; *see also* Brecher Dep. (Ex. 9) at 1038-39 (explaining that the SERM “concluded that the core data sheet needed to be changed” in light of Trials 126 and 127).

Within two weeks, AstraZeneca modified the Seroquel labeling to reflect this information; on June 22, 2007, AstraZeneca submitted a Changes Being Effected (“CBE”), supplement to FDA to present that new glucose data in Seroquel’s labeling. *See* June 22, 2007, Ltr. from AstraZeneca to FDA (Ex. 14) at 1-2; *see also* Brecher Dep. (Ex. 9) at 1038-41

433. Importantly, the minutes from the June 8, 2007 SERM meeting indicated that Dr. Ihor Rak, one of the presenters for AstraZeneca at both the April and June 2009 Advisory Committees, was also present at the June 8, 2007 SERM meeting that led to a CBE label change in just fourteen days:



Minutes

Chairman
Vikram Dev - VP and Head of CDS US

Date
08 June 2007

Page
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Participants
Eileen Carey - SERM Manager
Barry Arnold - EU Qualified Person
Judy Zander - Ex Dir US Safety Surveillance
Leigh Jefferies - GDSP Seroquel IR
Ron Leong - TASC
Martin Brecher - MSD
Julia Manning - Legal
Eileen Ming - Epidemiology
Liza DeAnnunzio - GDSP Seroquel XR
Xiang Ni - DS Physician
Susanne Fors - GRAD
Kathryn Bradley - AD Regulatory Labeling
Lisa Boomazian - Surveillance
Eva Alam - Surveillance
Linda Warner - Surveillance
Nina Dalillo - Surveillance
Tara Lee - Surveillance
Howard Hutchinson - CMO
Ihor Rak - VP Clin TA - NS
Sandi Raff - Sr Dir Clin Res

Secretary
Eileen Carey - SERM Manager

Apologies:
Michelle Dillone - Legal
Nina Sherak - Surveillance
Deborah Rolfe - Surveillance
Richard Hellmund - CIS
Janet Spiers-Alston - Global SERM Manager
Joachim Forsgren - VP CDS
Robert Williams - SERM Support
Stacy Forbes - SERM Administrator

SERM also recommended adding the following to Section 4.8 Undesirable Effects.

Frequency	System Organ Class	Event
Common (≥1% - <10 %)	Investigations	Blood glucose increased to hyperglycaemic level*

***Footnote**

Fasting blood glucose ≥126 mg/dL or a non fasting blood glucose ≥200 mg/dL on at least one occasion.

ACTION: Surveillance (Lisa Boomazian) and Medical Communications (Kevin Stansberry) will write the Clinical Overview.

Priority: B

Signal Source: Internal

Number of Signals: 1

Clinical Overview author(s): Kevin Stansberry and Lisa Boomazian

Due date for readiness of draft CO: 13 June 2007

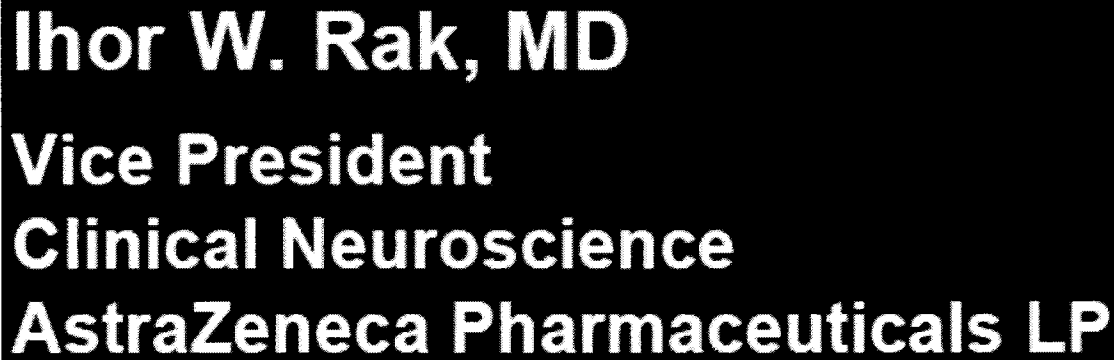
Core Data Sheet (CDS) author: Kathryn Bradley

Due date for CDS issue: 15 June 2007

Due date for Investigators Brochure issue: 31 July 2007

434. In June 2007, Dr. Rak's abbreviated title was "VP-Clin TA-NS".

435. According to AstraZeneca's presentation to the April 2009 Advisory Committee, in April 2009 Dr. Rak's title was:



Ihor W. Rak, MD
Vice President
Clinical Neuroscience
AstraZeneca Pharmaceuticals LP

436. As of April 2009, AstraZeneca was seeking approval for at least four new indications for Seroquel (for treatment of generalized anxiety disorder, as monotherapy in the treatment of major depression, for treatment of bipolar disorder in children and for treatment of schizophrenia in children).

437. The FDA rejected the applications for generalized anxiety disorder and monotherapy in the treatment of major depression due to safety concerns but nevertheless approved the pediatric applications.

438. The FDA subsequently approved Seroquel's use as an adjunct agent (alongside an antidepressant – including, but not limited to, citalopram, escitalopram, fluoxetine and sertraline) for the treatment of major depression.

439. Accordingly, AstraZeneca had a strong financial incentive to delay notifying the FDA of the QTc related label change in the United States' Seroquel labels until after the FDA had made its decisions regarding the pending applications.

440. On April 8, 2009, a meeting of the FDA's Psychopharmacologic Drugs Advisory Committee was convened to consider AstraZeneca's applications for indications for Seroquel XR for the treatment of major depressive disorder and generalized anxiety disorder.

441. The one outside expert who spoke at the April 8, 2009 hearing was Dr. Wayne Ray.

442. Dr. Ray was an epidemiologist from Vanderbilt University who published a study in January 2009 in the New England Journal of Medicine that showed that the use of quetiapine (and other atypical antipsychotics) was associated with an increased risk for sudden cardiac death that Dr. Ray attributed to the drugs' effect on the QT/QTc interval.

443. Despite the changes made to the Seroquel Core Data Sheet by April 2009 related to QT prolongation, AstraZeneca employee Dr. Ihor Rak made representations concerning "the entire quetiapine database" and quetiapine's effect on "cardiovascular events" that there were no cardiac safety issues associated with Seroquel. Dr. Rak stated:

Consistent with the preclinical, clinical and post-marketing data, the analyses discussed today do not identify a higher risk for sudden cardiac death associated with quetiapine as compared to placebo, and the data demonstrate that there is no difference in all-cause mortality between quetiapine and placebo.

In conclusion, we have looked across our entire quetiapine database, which included more than 26,000 patients in short and longer-term clinical studies across all indications and doses up to 800 milligrams per day. When considered in total, the risks of tardive dyskinesia, metabolic changes,

including cardiovascular adverse events, and sudden cardiac death have been well quantified within the limitations of the clinical program and provide sufficient data to inform the label, medication guide and risk management plans.

444. Despite the changes made to the April 2009 Core Data Sheet, Dr. Rak informed the committee that “the entire quetiapine database” indicated that the risk of “cardiovascular adverse events,” including QTc prolongation, “have been well quantified within the limitations of the clinical program and provide sufficient data to inform the label, medication guide and risk management plans.”

445. At the time Dr. Rak made this representation, there was no warning in the Seroquel labels related to the risks associated with the concomitant use of quetiapine with other QTc prolonging agents even though AstraZeneca had already changed quetiapine’s Core Data Sheet to include a specific warning about the use of quetiapine with QT/QTc prolonging drugs on April 1, 2009 (or a week before the April 8, 2009 FDA Advisory Committee.)

446. At no point in AstraZeneca’s presentation to the April 8, 2009 FDA Advisory Committee did AstraZeneca inform the Committee that it had changed the quetiapine Core Data Sheet to include numerous new warnings advising that “caution” should be used when quetiapine was used with other QT/QTc prolonging medications or the information that prompted that label change.

447. Despite the addition of specific warnings about the concomitant usage of quetiapine with QT/QTc prolonging drugs to the Seroquel Core Data Sheet on April 1, 2009, AstraZeneca employee’s Dr. Liza O’Dowd made the following statements to the FDA Advisory Committee on April 8, 2009:

When we looked at the AERS database, we looked at a couple of different trends. We looked at a bucket of seven cardiac death terms, very similar to that which we described in our briefing document. We also looked at terms which would suggest a potential proarrhythmic event. So we looked at the standard medical query for ventricular tachyarrhythmias.

As this panel I'm sure well understands, AERS data is good for signal generation. And what these numbers present is not absolute risk but rather look for signals of a potential event. So these numbers shouldn't be looked at -- only for signal detection, and that we look for numbers -- in AstraZeneca, we look at 1.8 events at signal detection.

So for sudden death terms with quetiapine, we have an EB05 of 1.21, which below the 1.8 level that we look at. Similarly for terms of ventricular tachyarrhythmias, we have an EB05 of .738. I could also tell you that the individual terms were 1.8 or below for all the individual PTs that contributed to these events.

You also asked for AERS data regarding cardiovascular events, and we can provide that data for you as well. And I can tell you the findings are actually very similar. There is no evidence of the signal. I'll get to the exact numbers in one second.

448. QT prolongation is a "cardiovascular event" specifically implicated in sudden cardiac death.

449. Consequently, AstraZeneca's own Safety Evaluation Review Meeting concluded that the Seroquel Core Data Sheet was deficient because it did not include a warning concerning the concomitant use of quetiapine with QT/QTc prolonging medications.

450. AstraZeneca employee Dr. Ihor Rak specifically stated at the April 8, 2009 FDA Advisory Committee that **"QT prolongation is recognized as a marker for increased risk of potentially serious ventricular arrhythmia and sudden cardiac death."**

451. FDA Advisory Committee member Dr. Robert Harrington, now a Stanford

cardiologist, also stated at the April 8, 2009 FDA Advisory Committee that **“[w]e know that QT prolongation is associated with sudden cardiac death.”**

452. At the time Dr. O’Dowd made her statements, AstraZeneca had changed its “Core Data Sheet” which Dr. Martin Brecher testified contained “those facts about the safety of [a] drug that **must be included in every label around that world,**” to include new warnings predicated, at least in part, on **QT prolongation rates in patients taking quetiapine that were nearly three times what was “expected” by the company.**

453. Assuredly, Dr. Harrington would have liked to know that AstraZeneca had decided to change the Seroquel and Seroquel labels to include new warnings about QT/QTc prolongation, what the warnings stated, and the reasons for the label change. All of this information was withheld from him, the other members of the FDA Advisory Committees in April 2009 (and a separate one in June 2009) and the entire FDA.

454. However, AstraZeneca did disclose this additional warning to the MEB on June 16, 2009.

455. As of April 1, 2009, AstraZeneca’s Corporate Integrity Agreement with the United States required that all of its “disclosures must be accurate and not misleading, with no material omissions.” Furthermore, AstraZeneca pledged that “[t]his policy applies to all information, whether favourable or unfavourable to AstraZeneca.” AstraZeneca’s 2008 Code of Conduct reads in relevant part:

AstraZeneca's policy is to disclose information in a timely manner, as necessary, to comply with all relevant legal and regulatory requirements. All such disclosures must be accurate and not misleading, with no material omissions. This policy applies to all information, whether favourable or unfavourable to AstraZeneca.

456. AstraZeneca employee Dr. Eric Michelson stated that, despite the fact that AstraZeneca amended the quetiapine Core Data Sheet just seven days prior to include new warnings about the dangers of using quetiapine with other QT/QTc prolonging agents – that quetiapine does “not prolong the QT”:

4 If you'll look at QT -- let me just point out
5 first that quetiapine itself does not prolong the QT.
6 It does not prolong the QT. However, when you take a
7 look at the effect on QT corrected for heart rate, it
8 does, using some methods, then project to cause small
9 changes, an increase in mean QT. And in this case,

457. Dr. Michelson further argued that quetiapine's effect on the QT/QTc interval was equivalent to haloperidol's, haloperidol's effect on the QT/QTc interval was equivalent to placebo therefore quetiapine's effect on the QT/QTc interval was equivalent to placebo. His testimony before the April 8, 2009 FDA Advisory Committee reads in relevant part:

Dr. Temple, can I just ask -- Dr. Garnett's not here. Dr. Stockbridge isn't here from your IOT committee.

Would you sort of concede that the effect that we have is essentially -- is indistinguishable from placebo as --

DR. GOODMAN: He doesn't have to answer that question.

458. Thus, despite Janssen's haloperidol label QT label change in March of 2007, an

FDA Safety Alert about haloperidol and QTc prolongation, the MEB calling Pfizer Study 054's conclusions into question, the FDA's Maryann Gordon suggesting that Dr. Laughren's position on haloperidol and QTc prolongation may be "erroneous," Pfizer concluding that haloperidol increased the QTc interval in a dose dependent manner, and the European Union concluding that there was "good" evidence supporting the cardiotoxicity of haloperidol, Dr. Eric Michelson argued that because haloperidol had a "placebo" like effect on the QTc interval in the April 2009 FDA Advisory Committee, thus Seroquel did, too.

459. At no point did anyone from AstraZeneca inform the members of either the FDA Advisory Committee about how regulatory authorities – both in the United States and Europe – had amended their view of haloperidol's effect on the QT/QTc interval.

460. Instead, in violation of its Corporate Integrity Agreement with the United States and numerous federal laws, AstraZeneca argued that haloperidol's effect on the QTc interval was equivalent to placebo, quetiapine's effect on the QT/QTc interval was equal to haloperidol and, therefore, Seroquel's effect on the QT/QTc interval was equivalent to placebo.

461. As of the September 2007 FDA Safety Alert, there was no scientific basis – whatsoever – for AstraZeneca to make such a claim. To make such an argument on April 8, 2009 was beyond the pale.

462. Furthermore, at no point did Dr. O'Dowd, Dr. Ihor Rak, or Dr. Eric Michelson – or any person from AstraZeneca – disclose the April 1, 2009 Core Data Sheet change to the April 8, 2009 FDA Advisory Committee, the reasons why the Core Data Sheet was changed or contents of the warning related to QT/QTc prolongation.

463. In fact, despite withholding the April 1, 2009 Core Data Sheet change from the FDA Advisory Committee, Dr. O'Dowd brazenly stated that AstraZeneca "didn't want to hide any data" from the Committee. Her remarks read in relevant part:

8 DR. O'DOWD: If I may, I wanted just to share
9 two things regarding the presentation that Dr. Ray had
10 this morning. One is, I thought it might be
11 informative for you to see the time to death for
12 patients who had cases adjudicated sudden cardiac death
13 within the quetiapine development program. And you can
14 see that we have, really, no clear pattern of when the
15 events occurred. We had one death within seven days of
16 starting therapy. We had five deaths, 7 to 30 days on
17 therapy, and 11 days after being on therapy for more
18 than 1 day. You'll note that this is not corrected for
19 exposure, though, so one must be careful when
20 interpreting these numbers. We also, for conservative
21 purposes, included all deaths we had in the database,
22 even if patients were off treatment. So, in fact, 6 of

1 the 23 quetiapine adjudicated deaths were actually off
2 therapy, but we included those since we didn't want to
3 hide any data. So I wanted to provide that for a
4 little bit of context.

464. In fact, AstraZeneca deliberately withheld from the Advisory Committee that the label had been changed, the reasons for the label change or the content of the new labeling information. All of this information was in AstraZeneca's possession by April 1, 2009.

465. One of the indications AstraZeneca was pursuing for Seroquel XR during the April 8, 2009 FDA Advisory Committee was its use for adjunct depression.

466. AstraZeneca studied Seroquel XR alongside studied alongside six different drugs associated with QT/QTc prolongation: citalopram, escitalopram, fluoxetine, venlafaxine, amitriptyline and sertraline.

467. In fact, in various Periodic Safety Update Reports over the years and at least one

letter published in a medical journal, AstraZeneca **itself** identified some of these drugs as ones causing QT/QTc prolongation, ventricular tachycardia or torsades de pointes as a way of explaining away reports of QT/QTc prolongation with quetiapine.

468. In a letter published in the November 2002 edition of the medical journal *Biological Psychiatry* authored by AstraZeneca physicians, including **Dr. Martin Brecher**, AstraZeneca attempted to dismiss a report of QTc prolongation associated with the use of quetiapine with lovastatin.

469. As the patient was also taking sertraline, the AZ employees stated that “**QT prolongation is listed as an adverse event for sertraline**” and that sertraline could have been a “possible cause of the reported QTc prolongation.”

470. In AstraZeneca’s September 14, 2002 Periodic Safety Report, it identified venlafaxine as a drug “labeled for prolonged QT interval”:

[REDACTED] This serious report of “Electrocardiogram QT prolonged” described an [REDACTED] patient who was receiving Seroquel for the treatment of confusion. Seroquel was gradually increased to 100 mg/day, and after two weeks of treatment the patient developed “cardio-respiratory arrest” and a prolonged QT interval (no value provided). Seroquel was discontinued and the events resolved the same day, without CPR. Medical history included coronary artery disease, prostatic cancer, and Parkinson’s disease. Concomitant medications included dexamethasone, Madopar (levodopa), aspirin, metoprolol, isosorbide, venlafaxine (labeled for prolonged QT interval), senna, and omeprazole. No further information was provided and additional information is not available.

471. In AstraZeneca’s September 20, 2006 Periodic Safety Update Report for Seroquel, it identified fluoxetine as a drug “for which QT prolongation has been reported”:

PSUR
Drug Substance quetiapine fumarate
Date 20 September 2006

Of the remaining 15 reports, one report (2006PK00569; also referenced in Section 9.5 *Drug interactions*) was confounded by both medical history (hypothyroidism, alcohol abuse) and a concomitant medication (fluoxetine) for which QT prolongation has been reported. Another

472. AstraZeneca's decision to change the quetiapine Core Data Sheets to advise "caution" with other QT/QTc prolonging medications like citalopram, escitalopram, fluoxetine, venlafaxine, amitriptyline, and sertraline **directly impacted** its adjunct depression indication. In the case of three of those drugs – venlafaxine, sertraline and fluoxetine – AstraZeneca stated itself that these drugs were associated with QT/QT prolongation.

473. On the question of whether "Seroquel XR has been shown to be acceptably safe as adjunctive treatment for major depressive disorder" the FDA Advisory Committee voted 6 to 3 in the affirmative.

474. Dr. Richard Malone, Professor of Psychiatry at Drexel University, stated that he "was kind of on the fence" but nevertheless voted yes. Dr. Sherry Kelsey, a Professor of Epidemiology at the University of Pittsburgh, voted yes stating that "given the risks and benefits, yes is my vote." Dr. Delbert Robinson, of the Feinstein Institute for Medical Research and Zucker Hillside Hospital,² voted yes stating "in balancing the risk-benefit, I think they would be acceptable in sort of an adjuvant situation."

475. We know, without question, that AstraZeneca concealed information from the Committee about the "safety profile" about quetiapine's use with these drugs and that the quetiapine labels on April 8, 2009 did not accurately reflect what AstraZeneca knew were the dangers associated with such usage.

476. This concealment of material evidence frustrated the Advisory Committee's efforts to conduct a **fully informed** "risk-benefit" analysis of the safety of the indication.

477. For the reasons explained above, Dr. O'Dowd, Dr. Michelson, and Dr. Ihor Rak's

² In a study of inpatient "sudden unexpected deaths" at **Zucker Hillside Hospital** covering 1984-2009, quetiapine was the only antipsychotic associated with a statistically significant increased risk of "sudden unexpected death" despite the fact that it was not on the market for thirteen of the twenty-five years the study encompassed. See Manu P. *Sudden Deaths in Psychiatric Patients*. *J Clin Psychiatry*. 2011 July; 72(7): 936-941.

testimony, violated 18 U.S.C. § 1001(1), 18 U.S.C. § 1001(2), 18 U.S.C. § 1001(3), 18 U.S.C. § 1001(4) and 21 C.F.R. 314.80(c)(2)(ii).

478. 18 U.S.C. § 1001's statutory terms are violated if someone:

1. "falsifies, conceals or covers up by any trick, scheme or device a material fact,"
2. "makes any false, fictitious or fraudulent statements or representations,"
3. "makes or uses any false writing or document knowing the same to contain any false, fictitious or fraudulent statement or entry"
4. and, for cases arising after the 1996 amendments, the item at issue was material.

479. Both Dr. O'Dowd's and Dr. Rak's false testimony to the April 8, 2009 FDA Advisory Committee made on behalf of AstraZeneca was material and false under 18 U.S.C. §1001.

480. 21 C.F.R. 314.80(c)(2)(ii) states as follows:

(ii) Each periodic report is required to contain: (a) a narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification number, adverse reaction term(s), and date of submission to FDA); (b) a FDA Form 3500A (Adverse Reaction Report) for each adverse drug experience not reported under paragraph (c) (1) (i) of this section (with an index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s)); and (c) a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).

481. AstraZeneca was required under statute and regulation to disclose to the FDA Advisory Committee that a labeling change related to QT prolongation had occurred, yet failed to do so.

482. In fact, in a document titled "Guidance for Industry, Formal Meeting with Sponsors and Applications for PDUFA Products - February 2000" the FDA stated that information provided to the FDA at PDUFA meetings must be the "**most current and accurate information available to the sponsor or applicant.**"

483. By withholding the April 1, 2009 Core Data Sheet change adding a warning about the dangers posed by the concomitant usage of quetiapine with QT/QTc prolonging medications, AstraZeneca withheld “the most current and accurate information available” to it about the safety of Seroquel and Seroquel XR.

484. On June 16, 2009, the MEB report for Seroquel was issued. The document reported the following:

- A study of quetiapine and asenapine was published and showed that quetiapine increased the QTc interval versus placebo 9.9 ms;
- Forty-four cases of Torsades de Pointes/QTc prolongation; and
- Seven cases of positive dechallenge and one case of positive rechallenge for patients taking quetiapine and experiencing QTc prolongation. The FDA defines positive rechallenge as “recurrence of signs and symptoms upon reintroduction of the product.”

485. On July 3, 2009, the study results from AstraZeneca quetiapine study “D1443L00023” were known to it. In this study, 2.67% of patients in the Seroquel XR arm and 5.8% of patients in the XR/lithium arm had QTc intervals ≥ 450 ms at the end of the study.

486. On July 13, 2009, a study of the measuring the mortality of Finnish patients taking antipsychotics was published in the journal Lancet.

487. The results of the study were that quetiapine had the highest risk of overall all-cause mortality (death) compared to the typical antipsychotic perphenazine among the second-generation antipsychotics (olanzapine, risperidone, clozapine, ziprasidone).

488. On August 1, 2009, AstraZeneca began the process of amending the European labels for Seroquel and Seroquel XR to include new warnings about QT/QTc prolongation. The label change in Europe was completed on October 31, 2009.

489. AstraZeneca delayed changing the label in the United States to include the new warning about the use of quetiapine with other QT/QTc prolonging medications until January 15, 2010.

490. On August 13, 2009, asenapine (“Saphris”) was launched in the United States with the same “should be avoided” label language the FDA imposed on the Seroquel/Seroquel XR labels in June 2011.

491. On September 15, 2009, AstraZeneca submitted another PSUR for both Seroquel and Seroquel XR to regulatory authorities, including the FDA.

492. In this PSUR, AZ provided an analysis of the FDA Adverse Event Database through the **fourth quarter of 2008** to determine the frequency of “events related to QTc prolongation” for Seroquel. The data analysis was performed for reports involving quetiapine as suspect or concomitant therapy.

493. In statistics, a result of “EB05 >1” indicates that there is an association between the drug and the event.

494. According to the FDA, “a drug-event combination having an **EB05>2** indicates 95% confidence that this drug-event combination occurs **at least twice the expected rate.**”

495. The September 15, 2009 AZ quetiapine PSUR reported AZ’s analysis of the FDA AERS database through the fourth quarter of 2008 for QTc prolongation as follows:

9.14.3 FDA AERS data

Events related to QT prolongation were used to search the FDA AERS database. The data analysis was performed for reports involving quetiapine as a suspect or concomitant therapy (see Table 48).

Table 48 FDA AERS database through 4Q2008: quetiapine and QT prolongation (suspect and concomitant)

Event	EB05 (N)
QT prolongation/torsade de pointes (narrow SMQ)	1.89 (246)
Electrocardiogram QT prolonged	2.80 (200)
Electrocardiogram QT interval abnormal	0.89 (3)
Long QT syndrome	0.74 (4)
Torsade de pointes	0.71 (23)
Ventricular tachycardia	0.67 (43)

AERS Adverse Event Reporting System EB05 lower boundary of the 90% confidence interval for the Empiric Bayesian Geometric Mean.
FDA Food and Drug Administration.

As shown in Table 48, the EB05 value for the narrow SMQ for “QT prolongation” was ≥ 1.8 . This suggests that there is a higher-than-expected association for QT prolongation with quetiapine, according to the FDA AERS data. When examining individual PTs, only the PT of “Electrocardiogram QT prolonged” had an EB05 ≥ 1.8 .

496. Events of “Electrocardiogram QT prolonged” in patients taking quetiapine occurred 2.8 times more frequently than expected.

497. As of September 15, 2009, neither the Seroquel nor the Seroquel XR labels contained a warning against the concomitant use of either drug with a drug known to increase QTc prolongation.

498. The November 2009 Seroquel label listed QTc prolongation as an “infrequent” event (occurring in 1/100 to 1/1000 patients) and stated that “comparisons for pooled-placebo controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportion of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and RR intervals.” Despite the April 1, 2009 change to the Seroquel CDS, there was no warning, whatsoever, about the dangers posed by the concomitant administration of quetiapine and other drugs known to cause prolongation of the QT/QTc interval.

499. The November 2009 label also made no mention of the results of the placebo-controlled Janssen study, the Merck study, Study 0013, Study 0015 or Pfizer Study 054.

500. DADS/DSHS Executive Formulary Committee minutes indicated that on December 28, 2009 an 18 year old Texas Medicaid beneficiary was admitted to a Texas state hospital for treatment of major depression. At the time of admission, the beneficiary was taking 600 mg of Seroquel at bedtime and 20 mg of citalopram in the morning. The complete narrative for this patient is as follows:

An 18-year-old female was admitted to a state hospital on December 28th for the treatment of major depression. Her medical conditions include obesity, self-reported osteoarthritis, and a history of asthma. Her labs on December 29th were within normal

limits except triglycerides 298 mg/dl and total protein 6.1 g/dl. The patient reported a history of polysubstance abuse, including alcohol and crack cocaine. No toxicology screens were obtained on admission as the patient had been continuously hospitalized since November 22nd at another facility. The patient had been taking quetiapine (Seroquel®) 600 mg at bedtime and citalopram (Celexa®) 20 mg in the morning and these were continued. Transdermal nicotine patches was added along with prns for ibuprofen (Motrin®) and **albuterol** (Ventolin®). An EKG was also ordered on admission. The EKG showed a prolonged QT (464 msec) and QTc (510 msec).

Following the EKG results, the quetiapine was discontinued and citalopram was increased to 40 mg daily. Trazodone (Desyrel®) was added to the patient's medication regimen. **A follow up EKG obtained on December 31st showed QT 420 msec, QTc 472 msec. Another EKG was obtained later and it showed improvement in the QT and QTc.** (emphasis added)

501. Once the quetiapine was discontinued, the EKG (a/k/a ECG) "showed improvement in the QT and QTc" interval. This report constitutes a positive dechallenge for quetiapine and QTc prolongation.

502. On January 15, 2010, AstraZeneca amended the Seroquel and Seroquel XR labels unilaterally, pursuant to the Changes Being Effected regulation, to include a statement that "caution" should be used when quetiapine is used concomitantly with drugs known to cause increases in the QTc interval.

503. That new warning read is relevant part:

-----**RECENT MAJOR CHANGES**-----

Warnings and Precautions. Use in Patients with Concomitant Illness (5.21), 01/2010

- **Drugs known to cause electrolyte imbalance or increase QT interval:** Caution should be used when quetiapine is used concomitantly with these drugs. (7)

5.21 Use in Patients with Concomitant Illness

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation in patients who overdosed on quetiapine [see *Overdosage* (10.1)], in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval [see *Drug Interactions* (7)]. Caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed with medicines known to cause electrolyte imbalance or increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e., the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesemia.

7 DRUG INTERACTIONS

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval [see *Warnings and Precautions* (5.21)].

504. In reliance upon the January 2010 label change, in July 2010 the Texas Medicaid Drug Use Review for Outpatient Use for quetiapine was amended to include a new warning concerning the use of quetiapine and QTc prolonging agents:

TARGET DRUG	INTERACTING DRUG	INTERACTION	RECOMMENDATIONS	CLINICAL SIGNIFICANCE
Quetiapine	QTc interval-prolonging medications	potential for increased cardiotoxicity (e.g., torsades de pointes, cardiac arrest) due to additive QT interval prolongation	avoid concurrent use; if combination necessary, closely monitor cardiac function; discontinue therapy in patients with QTc measurements > 500 msec	major (DrugReax) 1 (DIF) 1-severe, 2-major (Clinical Pharmacology)

505. The new warning directed that the “concurrent use” of quetiapine with other QT interval-prolonging medications should be avoided and that the interaction created a

“potential for increased cardiotoxicity (e.g., torsades de pointes, cardiac arrest) due to additive QT interval prolongation.” Furthermore, if such usage was necessary, Texas Medicaid directed physicians to “closely monitor cardiac function” and “discontinue therapy in patients with QTc measurements >500 msec.”

506. Importantly, this Medicaid Drug Use Review was prepared by was prepared by the Drug Information Service at the University of Texas Health Center at San Antonio and the College of Pharmacy at University of Texas at Austin.

507. In sum, Texas Medicaid amended its warnings after the January 2010 label change to direct that concurrent use of quetiapine with QTc interval-prolonging medications should be **avoided**.

508. On August 4, 2010, the FDA completed its review of the January 15, 2010 FDA label “Changes Being Effected” label change.

509. The FDA concluded that there was “no direct evidence of a direct correlation quetiapine/quetiapine XR and the adverse event of QT prolongation.” This standard was not the standard AstraZeneca was held to in determining whether or not to implement a Changes Being Effected label change.

510. Rather, C.F.R. 201.57 required AstraZeneca to revise its Seroquel labeling to “include a warning about a clinically significant hazard as soon as there is **reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established**.” (emphasis added).

511. The FDA physician commented that she saw no cases of “positive rechallenge” among the adverse event reports she reviewed.

512. The FDA defines a positive rechallenge as the “reoccurrence of similar signs and

symptoms upon reintroduction of the suspect product.” In the Review, the FDA stated that “there were **no reports of positive rechallenge**” in the adverse event reports for quetiapine.

513. As the FDA reviewer made a point to note this absence, the absence was a materially important element in reaching her conclusion that she did not observe “strong evidence of a direct correlation between quetiapine/quetiapine XR and the adverse event of QT prolongation.

514. However, in the June 16, 2009 MEB Dutch regulatory document there was one report of positive rechallenge. The FDA physician did not reference this report of a “positive rechallenge.” Consequently, this report was withheld from the FDA but not the Dutch regulatory authority.

515. In the Review, the FDA physician reviewed data to see if there was any “dose-response” relationship between quetiapine and QT prolongation. She stated that her review of the data provided by AstraZeneca “did not follow a linear dose-related signal.”

516. The June 16, 2009 MEB report stated that the head-to-head study between asenapine and quetiapine “showed QTc prolongation and a small relationship between QTc prolongation and plasma drug concentrations.” AstraZeneca was aware of this information prior to the date of this report.

517. On March 3, 2010, the Australian regulatory authority concluded that quetiapine and QT prolongation was “**dose dependent**” in children and adolescents and that QT prolongation in these patient populations was “more prominent” than in adults. AstraZeneca was aware of this information as of the date of this document.

518. On May 15, 2008, the FDA published an analysis of the head to head “thorough”

QT study of asenapine (“Saphris”) and quetiapine. The FDA reviewer speculated that the results of the study indicated that higher plasma concentrations of quetiapine in patients could translate into a QTc increase of **35 milliseconds**. As Saphris would be a direct competitor to quetiapine, AstraZeneca was aware of the information in this document as of the date of the document or shortly thereafter.

519. None of this evidence related to a “dose response” for Seroquel and Seroquel XR and QT prolongation was referenced by the FDA physician because AstraZeneca did not provide it to the FDA.

520. AstraZeneca conducted a review of the FDA AERs database through the fourth quarter of 2008 for reports of QT prolongation.

521. AZ concluded that “there is a higher than expected association with QT prolongation with quetiapine.” According to AstraZeneca, an “EB05³ greater than two suggests a possible association between the drug and the event.” According to the FDA, “a drug-event combination having an **EB05>2** indicates 95% confidence that this drug-event combination occurs **at least twice the expected rate.**” The “EB05” for quetiapine and QT prolongation through the fourth quarter of 2008 was **2.8**.

522. This evidence was not referenced by the FDA physician because AstraZeneca presumably withheld it from the FDA in its correspondence with the FDA concerning the January 15, 2010 CBE label change.

523. On December 4, 2006, Janssen published a multicenter, placebo and positive-controlled, randomized study between Seroquel and Invega/paliperidone (“Janssen study”). The study concluded quetiapine **caused a greater increase in QTc intervals than Invega.** This

³ EB05 – Empiric Bayesian Geometric Mean.

study was submitted to the FDA as part of Invega's New Drug Application (NDA 21,999) or shortly thereafter.

524. On December 19, 2006, the FDA concluded that Invega should have language included under the "Warnings" section of the label because it posed a "moderate risk" of QT prolongation.

525. On January 3, 2007, Invega was launched in the United States with the same "should be avoided" label language the FDA imposed on the Seroquel/Seroquel XR labels pursuant to its authority under the Food and Drug Administration Amendments Acts of 2007 (the "FDAAA") in June 2011.

526. Prior to the September 2007 passage of the FDAAA, FDA had no authority to impose new safety warnings on drugs.

527. As Invega was a competitor of Seroquel, AstraZeneca was aware of both Invega's label and all head-to-head studies of Invega and Seroquel.

528. None of evidence of quetiapine and QT prolongation was referenced by the FDA physician.

529. On August 1, 2008, Dr. Thomas Laughren, Director, Division of Psychiatry Products, published a review of Saphris. In his review, Dr. Laughren stated that "quetiapine had a roughly comparable effect on QT prolongation" as did Saphris.

530. He further stated that based upon the head-to-head study between quetiapine and Saphris "should have the standard warning for drugs with a modest QT prolonging effect." Dr. Laughren further stated "the prolongation of the QT interval appears to have vanishingly little clinical relevance in patients who are not co-administered drugs that prolong the QT interval."

531. On February 29, 2008, the FDA concluded its analysis of the “thorough” QT study of Saphris and quetiapine.

532. According to the FDA, the study of quetiapine with Saphris was a randomized, placebo-controlled, double blind, multicenter, parallel-group trial with 2 treatment periods. 40% of patients in the quetiapine arm of the study experienced changes in the QTcF interval ≥ 30 ms. One quetiapine patient also experienced changes in his QTcF interval ≥ 60 ms. No Saphris patients experienced changes in his QTcF interval ≥ 60 ms. Overall, the changes in the QTcF for Saphris were *less* than those observed for quetiapine.

533. On August 14, 2009, the FDA approved Saphris and its label. Curiously, the initial label included references to Seroquel’s effect on the QTc interval. The final labeling struck the references to quetiapine:

14.3 Thorough QT/QTc Trial

A trial assessing the potential QT/QTc prolonging effect of Sycrest[®] 5 mg, 10 mg, 15 mg, and 20 mg b.i.d. and placebo was conducted in 151 clinically stable patients with schizophrenia. Electrocardiographic assessments were performed throughout the dosing interval both at baseline and steady state. The mean increase in QTc from baseline at C_{max}, as derived from exposure response analysis, was 1.9 ms, 3.0 ms, 3.7 ms, and 4.9 ms for Sycrest[®] 5 mg, 10 mg, 15 mg, and 20 mg b.i.d., respectively; and 7.5 ms for quetiapine 375 mg b.i.d. There was a concentration-dependent increase in QTc interval. Categorical analyses for this study revealed that No patients treated with Sycrest[®] experienced QTc increases >60 ms from baseline measurements, nor did any patient experience a QTc of >500 ms. Additionally, there were no reports of Torsade de Pointes or any other adverse events associated with delayed ventricular repolarization.

534. On August 13, 2009, Saphris was launched in the United States with the “should be avoided” label language the FDA imposed on the Seroquel/Seroquel XR labels pursuant to its authority under the FDAAA of 2007.

535. None of this evidence of quetiapine and QT prolongation was referenced in the FDA Review because AstraZeneca presumably withheld it from the FDA in its correspondence related to the January 2010 CBE label change.

536. The FDA Reviewer’s label change recommendations were rejected in their

entirety when FDA imposed the “should be avoided” label change on the Seroquel and Seroquel XR labels in June 2011.

537. In March 2001, AstraZeneca amended its clinical trial exclusion criteria to **include** patients with QTcF ≥ 500 ms based upon “recent clinical data.”

538. In January 2003, AstraZeneca **excluded** patients from a study with QTc ≥ 450 ms and patients **who were taking QT prolonging medications (mirroring the June 2011 FDA imposed label change)**. In April 2004, AstraZeneca **excluded** patients from a study with QTc ≥ 450 ms in order “not to jeopardize patient safety. AstraZeneca’s decision to implement more stringent exclusion criteria in 2003 and 2004 was also predicated on “clinical data.”

539. This evidence of quetiapine and QT prolongation was not referenced in the FDA Review because AstraZeneca withheld it from the FDA.

540. The FDA physician also made a number of recommendations to weaken the QT warning in the Seroquel and Seroquel XR labels. However, **none** of the FDA physician’s labeling recommendations were implemented.

541. In fact, the FDA retained AstraZeneca’s January 2010 warnings until June 2011 when it implemented the more stringent “should be avoided” warning related to Seroquel and Seroquel XR and QT prolongation pursuant to its newly gained authority under the FDAAA.

542. Consequently, the FDA physician’s labeling recommendations from August 4, 2010 were rejected by the FDA itself.

543. On February 4, 2011, the FDA notified AstraZeneca of its decision to reject its January 2010 CBE label changes advising “caution” when quetiapine is used with QT/QTc prolonging medications (section 5.21 (Warnings and Precautions: Use in Patients with

Concomitant Illness) section 7 (Drug Interactions) and section 10 (Overdosage)). The letter read in relevant part:

These “Changes Being Effected” labeling supplemental new drug applications propose revisions to include text regarding QT prolongation associated with quetiapine overdose in the Highlights section, sections 5.21 (Warnings and Precautions: Use in Patients with Concomitant Illness), 7 (Drug Interactions), and 10 (Overdosage), as well as editorial revisions throughout labeling.

We have completed the review of your applications, as amended, and have determined that we cannot approve these applications in their present form. We request that you submit draft labeling that incorporates the revisions outlined in the attached labeling for Seroquel (NDA 020639). We request similar changes be made to the labeling for Seroquel XR (NDA 022047).

544. The FDA’s “revisions outlined in the attached labeling for Seroquel (NDA 020639)” and Seroquel XR included a warning that the use of quetiapine with other QT/QTc prolonging agents be “avoided.” Thus, the FDA strengthened the warnings related to quetiapine’s use with other QT/QTc prolonging medications from “caution” to “should be avoided.”

545. Thus, there is no evidence – whatsoever – that the FDA set a “ceiling” on the issue of providing a warning about Seroquel/Seroquel XR and QT/QTc prolongation.

546. On **August 23, 2010**, or seventeen days after the FDA Review, an AZ funded study of long term use of quetiapine titled “Efficacy and Tolerability of Extended Release Quetiapine Fumarate As Maintenance Treatment of Major Depressive Disorder: A Randomized, Placebo-Controlled Study” was published online in the journal *Depression and Anxiety*.

547. This study is known at AstraZeneca as the “Amethyst” study or Study 005. .

548. The authors stated that there “were no clinically relevant mean changes from baseline in the ECG, hematology, or clinical chemistry parameters.”

549. However, AZ documents from **January 29, 2008** from the **same study** indicated

that there was an “incidence of ≥ 60 bpm increase in QT interval corrected using Fridericia’s formula (QTcF)” of 4.1%.

550. Furthermore, the analysis stated that “ECG findings included a higher incidence of >15 bpm increases in heart rate and QTcF values ≥ 450 ms for the quetiapine XR group (10.2% and 2.5%, respectively) compared with the placebo group (6.6% and 0.3%, respectively).”

551. In sum, patients taking quetiapine XR were **eight times** more likely to experience dangerous QTc prolongation than patients taking placebo.

552. The results from the internal analysis were not reflected in the published study. Instead, the published study **falsely** stated that there “*were no clinically relevant mean changes from baseline in ECG, hematology, or clinical chemistry parameters.*”

553. Thus, even if the study were published at a date so that the FDA physician could look for evidence of QT prolongation with Seroquel and Seroquel XR, this study would have been of no use to her as AstraZeneca did not report the QT/QTc safety findings from the study accurately.

554. Neither State Drug Utilization Review Boards, nor the vendors it employs to help them monitor drug safety, were aware of the January 29, 2008 results.

555. The results of quetiapine’s effect on the QTc interval shown in this study were not provided to the April 8, 2009 FDA Advisory Board despite the fact that the Advisory Board was specifically concerned about the effects of **long term** use of quetiapine.

556. On February 15, 2012, the study results from AstraZeneca quetiapine study “D1443L00055” were published internally at AstraZeneca. The results showed that 2.35% of the patients in the quetiapine arm of the study developed “cardiac rhythm problems.”

557. In March 2012, a study titled “Sudden Death in Psychiatric Patients” was published in the *Journal of Clinical Psychiatry*.

558. The study’s objective was “to assess the cause and risk factors for sudden death discovered by contemporaneous investigation of all deaths occurring over a 26-year period (1984-2009) in adults receiving care in one large psychiatric hospital in New York.” The hospital is Zucker-Hillside Hospital in Queens, New York.

559. The study’s results were that the use of quetiapine was associated with a higher incidence of unexplained sudden death. These results were statistically significant.

560. Overall, quetiapine was found in 21.2% of all unexplained sudden deaths in the study and accounted for 48% of all unexplained deaths in the atypical antipsychotic class.

561. Significantly, quetiapine was only on the market for only thirteen of the twenty-six years that the study. Accordingly, quetiapine could not have been used at Zucker-Hillside Hospital because it was not commercially available until late 1997.

562. On April 4, 2013, a study titled “Antipsychotics and Torsadogenic Risk: Signals Emerging from the US FDA Adverse Event Reporting System Database” was published in the *Journal of Pharmacovigilance*.

563. The study analyzed reports of cardiac arrhythmia among antipsychotics from **January 2004 through December 2010**.

564. Of all the antipsychotics reviewed in the study, quetiapine had the highest number of **reported cases of sudden cardiac death with 468 reported during that time period**.

565. For **all but one** of the seven years this study analyzed, there was no warning – whatsoever – concerning the dangers posed by the use of Seroquel with QT/QTc prolonging drugs in the Seroquel and Seroquel XR United States labels.

566. Prior to the September 2007 passage of the FDAAA, the FDA had no authority to impose new warnings on pharmaceutical labels predicated on new safety information.

567. In June 2011, pursuant to its authority under the FDAAA, the **FDA** directed that the Seroquel label include the following language:

The use of quetiapine should be avoided in combination with other drugs that are known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, **methadone**). (emphasis added).

568. According to an October 2011 study published in the *International Journal of Clinical Psychopharmacology* titled “Comparative safety of antipsychotics in the WHO pharmacovigilance database: the haloperidol case” (“WHO study”), the difference in the reporting odds ratio for cardiac adverse events for haloperidol and quetiapine was not statistically significant.

569. In the WHO study, which analyzed cardiac adverse events for quetiapine, haloperidol, and olanzapine, **82%** of the cases of quetiapine associated cardiac adverse events were patients on **therapeutic** doses of quetiapine (800 mg or less).

570. In the WHO study, **60%** of the quetiapine-associate cardiac events were fatal.

571. **In reliance upon the June 2011 Seroquel label change**, in May 2012 the Texas Medicaid Drug Use Review for Outpatient Use was amended directing that the use of quetiapine with other drugs known to increase the QTc interval was now **contraindicated**:

Table 4 ^{2, 26, 37} Quetiapine Drug-Drug Interactions				
TARGET DRUG	INTERACTING DRUG	INTERACTION	RECOMMENDATIONS	CLINICAL SIGNIFICANCE
quetiapine	QTc interval-prolonging medications	potential for increased cardiotoxicity (e.g., torsades de pointes, cardiac arrest) due to additive QT interval prolongation	avoid concurrent use, if combination necessary, closely monitor cardiac function; discontinue therapy in patients with QTc measurements > 500 msec	contraindicated, major (DrugReax) 1 (DIF) 1-severe, 2-major (Clinical Pharmacology)

**contraindicated, major (DrugReax)
1 (DIF)
1-severe, 2-major (Clinical
Pharmacology)**

572. Importantly, this Medicaid Drug Use Review was prepared by the Drug Information Service at the University of Texas Health Center at San Antonio and the College of Pharmacy at University of Texas at Austin and employees of these institutions are state employees.

573. Upon information and belief, all State Medicaid agencies prepared, or had prepared for them by vendors, similar drug use reviews wherein the use of quetiapine with QT/QTc prolonging medications was contraindicated.

574. Upon information and belief, all State Medicaid agencies have determined that the use of quetiapine (Seroquel or Seroquel XR) is now contraindicated when used with other QTc prolonging medications.

575. When an attempt is made to fill two drugs that are contraindicated together for a Medicaid beneficiary, the pharmacist receives a National Council for Prescription Drug Programs ("NCPDP") error code "75" indicating that **before the prescriptions will paid for,** and filled, a prior authorization must be completed and approved by the Medicaid authorities.

576. The aforementioned 2003 OIG Medicaid Cost Containment Report stated that State Medicaid prior authorization programs require "State-sanctioned approval before particular drugs can be dispensed" and that physicians should be "discourage[ed] from prescribing these drugs unless medically necessary."

577. The use of quetiapine with another drug known to increase the QTc interval is

now classified as a code “1” drug interaction. In New York, and in all other States, whenever a code “1” drug-drug interaction is identified during a prospective drug review, the prescription is automatically rejected:

eMedNY

Prospective Drug Utilization Review/ Electronic Claims Capture and Adjudication ProDUR/ECCA Provider Manual

Clinical Significance

The Clinical Significance is a code that identifies the severity level and how critical the conflict. The following chart lists each drug conflict code and the clinical significance codes which may be returned for that code as well as whether they are DUR rejects or warnings.

Conflict Code	<u>Reject/</u> Warning	Clinical Significance	Description of Clinical Significance
DD Drug-Drug	<u>R</u>	1	Most significant. Documentation substantiates interaction is at least likely to occur in some patients, even though more clinical data may be needed. <u>Action to reduce risk of adverse interaction usually required.</u>

Reason for Service Code	<p>When a claim is denied due to one or more of the following DUR Conflict Codes, <u>each must have an appropriate DUR reject override for the claim to pay.</u></p> <p> TD = Therapeutic Duplication ER = Drug Overuse DD = Drug to Drug Interaction NP = New Patient Processing AD = Additional Drug Needed PN = Prescriber Consultation </p>
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578. The California Medicaid program is called Medi-Cal. The Medi-Cal Drug Utilization and Review Committee is responsible for “developing policy for monitoring and controlling therapeutically inappropriate drug utilization” as well as “setting standards to

serve as guidelines on misprescribing, overprescribing, and contraindicated drug use, and protocols for informing prescribers of inappropriate prescribing.”

579. As of October 3, 2011, all antipsychotics, including quetiapine, require a prior authorization before the prescription is filled in Alabama. The top reason for denial of a prior authorization for an antipsychotic, and thus denial of payment for the drug, was “poly-pharmacy” which indicates that Alabama was aware of, and acted upon, the June 2011 Seroquel label change.

580. In June 2002, the State Drug Utilization Board in Indiana required that drug claims that post a “severity level 1 drug-drug interaction will be denied” and that “prescribers must substantiate the need to dispense the products that are contraindicated for simultaneous use before PA (prior authorization) will be granted.” The Indiana State Medicaid document from June 2002 reads in relevant part:

Drug-Drug Interaction

Claims that post a severity level 1 drug-drug interaction will be denied.

Prescribers must substantiate the need to dispense the products that are contraindicated for simultaneous use before PA will be granted.

581. Today in Indiana, before a claim for contraindicated drugs is approved and paid the physician must complete a prior authorization request that includes “a clinical rationale and monitoring plans for the co-administration of contraindicated drug products” and Indiana Medicaid must approve that request. The relevant Indiana Medicaid document reads in relevant part:

**INDIANA HEALTH COVERAGE PROGRAMS (IHCP) PHARMACY BENEFIT
PBM CALL CENTER PRIOR AUTHORIZATION REQUEST FORM**

Please check applicable categories:

☐ Severity Level 1 Drug-Drug Interaction

☐ Other _____

Please add a brief summary that would help document the need for the above listed medications.

Clinical Summary: A current plan of treatment and progress notes may be requested for documentation.

Note: For Severity Level 1 Drug-Drug interactions please provide clinical rationale and monitoring plans for the co-administration of contraindicated drug products. Certain other products (e.g. Synagis) have specific prior authorization forms found at: <http://www.indianamedicaid.com/ihcp/Publications/forms.asp>

582. Barring such careful consideration and monitoring of the risks and benefits associated with using drugs that are contraindicated with one another, the use of two drugs together that are contraindicated (i.e., quetiapine and another QTc prolonging drug) cannot be for a “medically accepted indication” (under 42 U.S.C. §§ 1396r-8(k), (g)(1)(B)(i)) because the risk of using two (or more) drugs together that are contraindicated, according to FDA, “clearly outweighs any possible therapeutic benefit.”

583. Accordingly, AZ’s deliberate, willful and reckless decision not to amend the quetiapine labels to include a warning about Seroquel’s effect on the QTc interval AZ caused physicians to prescribe, pharmacists to fill, and State Medicaid agencies to approve payment for, Seroquel prescriptions with drugs known to prolong QTc.

584. If AZ had amended the quetiapine label when it knew it was associated with QTc prolongation in 1997, physicians would neither have prescribed nor pharmacists filled Seroquel prescriptions with drugs known to prolong the QT/QTc interval.

585. Furthermore, Drug Utilization Boards, like New York and California’s, would have protected their Medicaid beneficiaries by finding that such use is “contraindicated” and would have refused payment for such concomitant usage unless a physician filed a prior authorization request that specifically asked for the use of two contraindicated drugs.

F. Seroquel’s effect on active duty military personnel

586. In September 2011, the results from a study of **active duty soldiers** taking

quetiapine were published and showed that QTc prolongation was a “**common finding**” in patients taking quetiapine.

587. Ten patients, constituting **8%** of the **active duty soldiers** who received ECGs, developed Seroquel-induced QTc prolongation. One developed QTc prolongation not attributed to Seroquel. All of the soldiers’ Seroquel-induced QTc prolongation resolved upon discontinuation of Seroquel. **Each of these ten cases constituted a positive dechallenge.**

588. Only one of the eleven reports of QTc prolongation was not attributed to the ingestion of Seroquel.

589. An abstract of the study reads in its relevant part:

Results: 692 Active Duty Soldiers received initial prescriptions for quetiapine during the study period. The most common indications for quetiapine prescription were insomnia (60%), anxiety (19%), mood disorders (12%) and PTSD (8%). Only 3.4% received quetiapine for an FDA-approved indications. The average Soldier experienced a 9 pound weight gain at 24 months. Compliance with screening for diabetes and QTC prolongation was poor at 52% and 18%, respectively. None of the Soldiers who received screening met criteria for diabetes. 126 underwent an EKG after starting quetiapine, eleven (9%) had prolonged QTc durations.

Conclusion: Quetiapine is most commonly prescribed for non-FDA approved indications with insomnia and anxiety as the most frequently associated diagnoses. The majority of soldiers gained weight while on this medication. Prolonged QTc was a common finding. Prescribers of quetiapine should adhere to the recommended screening parameters to minimize risks associated with this medication and ensure their patients undergo appropriate counseling regarding side effects.

590. Importantly, despite these and other findings regarding Seroquel’s effect on the QT interval (including, but not limited to, AstraZeneca Studies 13, 15, 28, 49, 93, 112, 135, 149, 150, the Merck study, the Janssen study, Pfizer Study 054, and the National Institute of Mental Health funded CATIE study), the Seroquel label states that QT prolongation is “infrequent” and occurs in only 1/100 to 1/1000 patients who take quetiapine.

591. Many active duty soldiers, airmen, sailors, marines and veterans have received

Seroquel for the treatment of PTSD and other off-label purposes. AZ funded all of the studies that the Department of Defense and the Veteran's Administration relied upon to prescribe Seroquel for this off-label purpose.

592. Importantly, by August 27, 2008, AZ knew that another of its AZ-funded Seroquel PTSD studies, titled AU-SEA-006, showed that Seroquel was *ineffective* in treating PTSD. However, AZ **failed to disclose the results of this study to either the Veteran's Administration or the Department of Defense.**

593. On February 22, 2012, the Assistant Secretary of Defense for Health Affairs Jonathan Woodson issued a guidance letter to the Assistant Secretaries of the Army, Navy and Air Force titled "Guidance for Providers Prescribing Atypical Antipsychotic Medication." The Surgeons General for the Army, Navy, and Air Force as well as the Medical Officer for the Marine Corps were also copied on this letter.

594. In this guidance letter, Assistant Secretary Woodson reported that during fiscal year 2010 Seroquel had been prescribed to 1.7% of all active duty Army personnel and 0.7% of all active duty Marine personnel. Accordingly, approximately 9,201 active duty Army service members and 1,353 active duty Marines were prescribed Seroquel during fiscal year 2010.

595. Assistant Secretary Woodson advised that "[p]roviders should **use caution** when these agents are used as sleep agents in SMs (service members) with substance use disorders, especially given the risk of such side effects as glucose dysregulation and **cardiac effects.**"

596. Furthermore, Assistant Secretary Woodson directed that "MTF Commanders and clinical leaders [be] **cognizant of the factors associated with the use of atypical antipsychotics and ensure that they have systems in place to monitor prescription and**

utilization patterns throughout their network, including the use of off-label atypical antipsychotics.”

597. On March 28, 2012, the U.S. Central Command removed Seroquel from its “approved formulary” based on concerns of cardiac safety.

G. Seroquel’s effect on the elderly

598. On June 6, 2000, the results from AstraZeneca’s Study 49 were published internally at AstraZeneca.

599. Study 49 was titled “A Multi-Centre, Double-Blind, Randomised, Parallel-Group Comparison of Quetiapine and Haloperidol in the Treatment of Elderly Patients Presenting with Dementia and Psychosis.”

600. The “key exclusion criteria” for this study was:

Key exclusion criteria: Evidence of any significant clinical disorder or laboratory finding for this age group; patients with a history or clinical evidence on ECG of myocardial infarction within the last 3 months, or any clinically significant ECG result; total white blood cell count less than the lower limit of the reference range of the laboratory used for haematological monitoring; history of drug-induced agranulocytosis; satisfaction of diagnostic criteria for delirium superimposed on dementia.

601. Accordingly, no patient presented with “any clinically significant ECG result” when entering this study.

602. During the course of this study, 7.4% of the patients in the quetiapine arm of the study experienced “[s]ignificant ECG changes.”

603. In October 2000, two AstraZeneca employees – Vikram Dev and Joher Raniwalla’s “Review Article” (“Dev-Raniwalla article”) was published in the journal *Drug Safety*.

604. In the Dev-Raniwalla article, despite the authors presumably knowing the results

of Study 49, the authors described the effect of quetiapine in the elderly patient population as “benign”:

6. Use in Special Populations

6.1 Elderly

The benign profile of quetiapine makes it suitable for the elderly, who are particularly sensitive to the extrapyramidal effects of antipsychotics.^[53] Clinical experience of quetiapine in elderly patients is increasing and data obtained from clinical trials show quetiapine to be well tolerated in this population.

605. Furthermore, the Dev-Raniwalla article, despite the fact that the authors presumably knew the results of Study 49, the authors stated that “preliminary data show quetiapine to be very well tolerated in the elderly” and “the benign adverse effect profile of quetiapine predicts that it will be advantageous for patients with schizophrenia, including those who are especially sensitive to adverse effects from medications, such as the elderly and patients in poor general health.”

606. In the September 29, 2004 PSUR AstraZeneca reported the existence of Study 46:

PSUR: Appendix D
Drug Substance: quetiapine fumarate
Date: 29 September 2004

5077US/0046

A multi-center, Double-blind, randomized comparison of the efficacy and safety of quetiapine fumarate (SEROQUEL) and placebo in the treatment of agitation associated with dementia

CTR
Pending

607. In Study 46, 241 patients were assigned to Seroquel and 92 were assigned to placebo.

608. The results of this study were presented at the International Conference on Alzheimer's Disease and Related Disorders held in Philadelphia, Pennsylvania from July 17-22, 2004.

609. The results of the study were that 16 of the 241 patients who received Seroquel **died** during treatment whereas only 3 of the 92 patients taking placebo did.

610. These results between the Seroquel and placebo arms in the study were statistically significant.

611. This study was never published in any journal.

612. Instead, AstraZeneca released a synopsis of the study that reads in relevant part:

Results: The baseline characteristics of patients (n=333) were comparable among treatment groups and 63-65% completed the entire study. Compared to placebo, quetiapine 200 mg/day was associated with statistically significant improvements in PANSS-EC and CGI-C scores, and significantly higher response rates ($p < 0.05$ for all measures). No CVAEs were reported in either quetiapine group. The incidences of postural hypotension and falls were similar among all treatment groups.

Conclusions: Quetiapine 200 mg/day is effective and well tolerated in treating patients with agitation associated with dementia.

Word count (maximum of 200) = 199

613. There is no mention – whatsoever – of the statistically significant higher rate of death in the patients taking Seroquel in this study. Instead, it states that “[q]uetipaine is effective and well tolerated in treating agitation associated with dementia.”

614. On April 11, 2005, the quetiapine label (and the labels for other atypical antipsychotics) received a “Black Box” warning from the FDA regarding the use of quetiapine in patients suffering from dementia-related psychosis that specifically references an increased risk of “heart failure” and “sudden death”:

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SEROQUEL safely and effectively. See full prescribing information for SEROQUEL.

SEROQUEL (quetiapine fumarate) Tablets

Initial US Approval: 1997

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA See Full Prescribing Information for complete boxed warning.

- Antipsychotic drugs are associated with an increased risk of death (5.1)
- Quetiapine is not approved for elderly patients with Dementia-Related Psychosis (5.1)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. SEROQUEL (quetiapine) is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions* (5.1)].

615. Heart failure and sudden death are two of the consequences of clinically significant QTc prolongation.

616. Despite this Black Box Warning and the inherent dangers associated with the use of quetiapine in the elderly, AstraZeneca continues to direct and incentivize sales representatives to promote Seroquel XR to geriatric psychiatrists.

H. Seroquel's effect on the QT/QTc interval in children and AZ's violation of Federal laws

617. In October 2002, an AstraZeneca funded study titled "A Double-Blind, Randomized, **Placebo-Controlled** Study of Quetiapine as Adjunctive Treatment for Adolescent Mania" was published in the *Journal of the American Academy of Child and Adolescent Psychiatry*.

618. Although the study reported that "no subjects developed...ECG abnormalities," the quetiapine arm of the study increased the QTc interval by an average of 7 ms with one patient experiencing a **21 ms increase** in his/her QTc interval.

619. In its June 16, 2004 report, MEB described the results from this same ten patient study. Three (30%) ECG abnormalities were found including two cases of QT prolongation and one intermittent first degree AV-block with possible ventricular hypertrophy. The MEB's report reads in relevant part:

Another article described an open-label, single site study investigating the extended use of quetiapine in 10 adolescents with schizoaffective or bipolar disorder following a PK study and assessed the long-term safety, tolerability and efficacy of quetiapine. AEs reported in this study were somnolence, headache and pharyngitis. Three ECG abnormalities were found: two QT-prolongations and one intermittent first degree AV-block with possible ventricular hypertrophy. The authors concluded that quetiapine was effective in these adolescents and demonstrated a favourable long-term safety and tolerability profile.

620. The aforementioned study, titled "Long-Term Safety, Tolerability and Clinical Efficacy of Quetiapine in Adolescents: An Open-Label Extension Trial" was published in the *Journal of Child and Adolescent Psychopharmacology* in November 2003.

621. Importantly, three of the co-authors of the study, Lynn Carrero, MBA, Dr. Dennis Sweitzer, PhD. and Larry Potter, M.S. were employees of AstraZeneca.

622. Although there were no disclosures concerning what entity funded this study, the fact that three of the authors were AstraZeneca employees indicates that AstraZeneca funded this study.

623. On December 14, 2004, a document titled "Safety Query Response: Review of All Pediatric Reports for Seroquel (quetiapine fumarate) Through September 30, 2004" was published internally at AstraZeneca ("The Safety Query Response").

624. The Safety Query Response contained a report of an eight year old boy who developed QT prolongation while taking 25 mg a day of Seroquel. The QTc prolongation resolved upon discontinuation of Seroquel. This report constitutes a positive dechallenge for Seroquel and QT prolongation:

Table 58 Reports of QT prolongation age 2 to 11 and 12 to 18; medically confirmed (7 reports)

Report #/ Preferred term	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2003UW09322 Non-serious	8/M	25 mg/d ay/ 1 year	Anxiety, depression, enuresis, ADHD, bizarre thoughts	Bupropion, desmopressin	PTs: ECG QT prolonged. Pt had prolonged QT (444 msec). Seroquel D/c'd. Pt rec'd (QT=427 msec) about 1 month later. No palpitations, dizziness, syncope, cardiac arrest. No baseline or other info provided.

625. The Safety Query Response contained a report of a seventeen year old girl who developed QTc prolongation while on Seroquel that was **confirmed by a cardiologist**:

Table 58 Reports of QT prolongation age 2 to 11 and 12 to 18; medically confirmed (7 reports)

Report #/ Preferred term	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2004UW02024 non-serious	17/F	200 mg/ day/ TTO unk	Not provided	Not provided	PTs: Electrocardiogram QT corrected interval. Occurred during ECG as routine care. Physician referred Pt to cardiologist who confirmed prolonged QT. Seroquel D/c'd. No outcome or further info.

626. Curiously, AstraZeneca concluded that this report contained “scant clinical detail” that did not lend itself to analysis despite the fact that the QT prolongation **was confirmed by a cardiologist**.

627. The Safety Query Response contained a report of a sixteen year old girl who was diagnosed with QT prolongation after complaining of **chest pain** while taking Seroquel:

Table 58 Reports of QT prolongation age 2 to 11 and 12 to 18; medically confirmed (7 reports)

Report #/ Preferred term	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2003UW11369	16/F	300 mg/ day/unk	Overdose while on Seroquel 2 yrs prior, food allergy	Sertraline, bupropion	PTs: ECG QT prolonged, Chest pain. Pt c/o chest pain; an ECG was performed. Prolonged QT identified. No data provided. No treatment or whether Seroquel was cont's provided. No further info provided.

628. Curiously, AstraZeneca concluded that this report contained “scant clinical detail” that did not lend itself to analysis despite the fact that the patient’s QT prolongation was confirmed by an ECG and the patient complained of chest pain (a symptom of QT prolongation).

629. The Safety Query Response contained a report of a sixteen year old girl who experienced **palpitations, increased blood pressure and QT prolongation** while on Seroquel. All of these adverse events resolved upon discontinuation of Seroquel. This report constitutes a **positive dechallenge** for Seroquel and QT prolongation:

Table 58 Reports of QT prolongation age 2 to 11 and 12 to 18; medically confirmed (7 reports)

Report #/ Preferred term	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	PTs/Comments
2003GB00456 serious	16/F	175- 200 mg/ day/ 17 days	Not provided	Not provided	No further info provided. PTs: ECG QT prolonged ^b , palpitations, blood pressure increased, constipation. Had AE 17 days after starting Seroquel + discontinuing risperidone. Seroquel D/c'd. All AEs resolved.

630. Curiously, AstraZeneca concluded that this report contained “scant clinical detail” that did not lend itself to analysis despite the fact that the patient’s symptoms (QT prolongation, palpitations (a symptom of QT prolongation) and increased blood pressure) **all resolved with the discontinuation of Seroquel and constituted a positive dechallenge.**

631. The June 16, 2008 report from the MEB described the reports of 222 “medically-confirmed non-legal reports in patients younger than 18 years of age (134 serious and 187 non-serious)” were retrieved for the “period under review” or August 1, 2006 through July 31, 2007. QTc prolongation is described as an “unlisted adverse reaction” and QTc prolongation had been reported at least six separate times in patients under the age of 18. The MEB report reads in relevant part:

Special patient groups

During the period under review 222 medically-confirmed non-legal reports in patients younger than 18 years of age were retrieved (134 serious and 187 non-serious). Two of the 222 patients were <2 years of age (see also above), 60 were between 2-11 years or identified as a child and 160 were between the ages of 12-18 years or identified as an adolescent. Seven of the cases had a fatal outcome (see also above). Unlisted reactions reported more than once in children 2-11 years of age were urinary retention (2), QTc prolongation (2) and diabetes mellitus (2). Unlisted reactions in adolescents reported more than once were (overdose cases and fatal cases excluded) hyperprolactinaemia (4), epistaxis (3), rash (2), tic (2), cataract (2), lymphocyte count increased (2), hypothyroidism (2), chest pain (2), pyrexia (2), drug screen positive (2), dyspnoea (2), anger (2), and coma (2). Many other unlisted adverse reactions were reported once in this age group including QTc prolonged.

632. In the communications between the MEB and AZ, AZ “notes the safety and efficacy profile of quetiapine will be updated as the double-blind, placebo-controlled trials involving pediatric patients are completed.” The MEB report reads in relevant part:

The MAH notes the safety and efficacy profile of quetiapine will be updated as the double-blind, placebo-controlled trials involving paediatric patients are completed. The first trial has been completed and the results described above. (The findings of this study will be examined in the ongoing long-term 6-month extension study). The other trials are expected to finish in 2Q2008 and 3Q2009.

Assessor's comment: Many unlisted adverse reactions were reported in use in children and adolescents during the current PSUR and earlier PSURs. The MAH in updating safety information on children/adolescents should not only take the results of the above mentioned studies into account but also the cumulative post-marketing reports involving this special patient group.

633. The referenced “first trial” is Study 149 and its “ongoing long-term 6-month extension” is Study 150.

634. The referenced “other trials” are Study 28 and Study 112.

635. While attempting to gain an indication for the use of quetiapine in children, AZ

failed to disclose certain information to the FDA concerning Seroquel's effect on the QTc interval in children in AZ's 2009 Briefing Document titled "Briefing Document for Psychopharmacologic Drugs Advisory Committee" and AZ's June 9-10, 2009 presentation to the FDA .

636. AZ also failed to present this information to State Drug Utilization Boards.

637. In Study 28, a study of the pharmacokinetics of quetiapine in children with schizophrenia, schizoaffective disorder or bipolar disease, 7.7% of patients aged 10-12 experienced "ECG QT corrected interval **prolonged**." Overall, 3.7% of patients experienced this adverse event in the study.

638. One patient discontinued treatment in Study 28 because of a prolonged QT interval.

639. Curiously, in a document titled "A Study to Characterize the Steady-State Pharmacokinetics, Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) in Children and Adolescents with Selected Psychotic Disorders" (Study 28) AstraZeneca reported that "[m]ean changes in QTc tended to be small **decreases**":

Clinical Study Report Synopsis
Drug Substance quetiapine fumarate
Study Code D1441C00028

There were no apparent trends over time in QTc intervals. Mean changes in QTc tended to be small decreases (which were not clinically meaningful), rather than increases. There were no clinically significant QTc intervals or changes from baseline in QTc intervals.

640. Despite AstraZeneca's position that there were "no clinically significant QTc intervals or changes from baseline in QTc intervals," QTc increased in a **dose dependent** manner for all of the subjects in the study.

641. In Study 150, a study of quetiapine in children and adolescents with Bipolar I

disorder and adolescents with schizophrenia, five patients experienced six adverse events potentially related to QTc prolongation. Adverse events potentially related to QTc prolongation include, but are not limited to, **tachycardia** (rapid heartbeat), **syncope** (a sudden loss of consciousness), near syncope, chest pain, **hypotension** (low blood pressure), dizziness, light-headedness, seizure (due to cerebral hypoxia), palpitations, dyspnoea (shortness of breath), TdP and sudden death.

642. Study 150 was the six month extension study for Study 149. On September 17, 2007, AZ reported the following results from Study 149:

Clinical studies and pharmacoepidemiology program

There were two newly analyzed clinical studies (D1447C00126, D1447C00127) with significant safety information during the PSUR period, which led to a CDS update regarding blood glucose increased to hyperglycemic level.

Additionally, a pediatric study (Study D1441C00149) completed during the reporting period. The findings in this study are quite similar to the ones seen in adults, however, some differences existed. Based on the short duration of this study (three weeks), it is difficult to assess the importance of these differences. There were a number of safety findings that possibly indicated a higher incidence in quetiapine-treated patients. These included abnormal laboratory parameters (glucose, ANC, lipids, thyroid, ALT, prolactin), syncope, tachycardia, blood pressure, weight, sedation/somnolence, and suicidality, that will need to be examined in the ongoing long-term, six month, extension study (Study D1441C00150) in order to determine whether children and adolescents are more vulnerable to these safety issues than adults. This safety data will be reviewed at an internal high level safety review meeting to consider inclusion in the SEROQUEL/SEROQUEL XR CDS.

643. The specific results related to cardiac effects of quetiapine in children were as follows:

Several patients experienced changes in blood pressure over the course of this study. In the 600 mg quetiapine group, 1 patient experienced an AE of hypertension, and a second patient experienced an AE of orthostatic hypotension. In the 400 mg quetiapine group, 1 patient reported an AE of hypotension. Nineteen patients experienced a potentially clinically low supine or standing systolic or diastolic BP; 6 in the 400 mg quetiapine group, 7 in the 600 mg quetiapine group, and 6 in the placebo group. Four quetiapine-treated patients experienced syncope, of which two withdrew from the study because of the syncopal AE.

644. Consequently, in Study 149, there was a higher incidence of syncope, tachycardia and abnormal blood pressure (including hypotension) in quetiapine treated patients. Each of these adverse events is associated with QTc prolongation.

645. Furthermore, three of the four patients who experienced syncope in Study 149 were female with two of the four experiencing adverse events associated with syncope. A 12 year old boy experienced vomiting and nausea in the 400 mg quetiapine group and a 12 year old girl experienced “vomiting, headache and blurred vision.”

646. 1.3% of the patients in Study 150 experienced adverse events related to QTc prolongation.

647. When Study 150 was published in October 2013, or over four years after AZ presented the data to the June 2009 FDA Advisory Committee, it was reported that five patients developed QT prolongation >500 ms:

ECG-related AEs that were reported by more than one patient included tachycardia ($n=19$ patients), sinus tachycardia ($n=5$), bundle branch block ($n=3$), and prolonged QT ≥ 500 msec ($n=5$). All patients with prolonged QT had normal QTc (Fridericia) intervals below the 450 msec cutoff (range 412–445 msec).

648. Importantly, and despite these results, at the April 8, 2009 FDA Advisory Committee meeting Dr. Eric Michelson stated definitively that quetiapine did not “prolong the QT interval.”

649. Rather than disclose these results to the June 2009 Pediatric Advisory Committee, AZ stated – falsely – that no patients developed QT prolongation greater than 500 ms.

650. In her prepared remarks to the June 2009 Pediatric Advisory Committee, Dr. Eliza O’Dowd stated:

The final topic we will discuss today is ECG findings. In the clinical development program, centrally-read ECGs were obtained during the studies. Decreases in QTc Fridericia, or QTcF were seen both for quetiapine and placebo, with a quetiapine-placebo difference of 0.5 milliseconds. Importantly, there were no increases in QTcF greater than 60 milliseconds, or shifts greater than 500 milliseconds, nor were there any adverse events of ventricular arrhythmias reported in the short- or longer-term pediatric studies.

651. Based on the results of Study 150 known to AstraZeneca at that time, the statement that there were no “shifts greater than 500 milliseconds” was both a material and false statement to the June 2009 Pediatric Advisory Committee.

652. Despite the passage of over two months, at no point in AstraZeneca’s presentation to the June 2009 FDA Advisory Committee did AstraZeneca inform the Committee that it had changed the quetiapine Core Data Sheet on April 1, 2009 to include numerous new warnings advising that “caution” should be used when quetiapine was used with other QT/QTc prolonging medications, what the warnings would be or the information that prompted that label change.

653. Instead, AstraZeneca affirmatively stated that the quetiapine label (both Seroquel and Seroquel XR) were accurate for children, adolescents and adults as of June 8-9, 2009 in its presentation to the pediatric advisory committee despite the fact that AstraZeneca had amended the quetiapine label to include new warnings about the concomitant usage of quetiapine with other QT/QTc prolonging medications on April 1, 2009:

**Seroquel® (quetiapine fumarate) for
Treatment of Pediatric Patients With
Bipolar Mania (10 - 17 Years) or
Schizophrenia (13 - 17 Years)**

**United States Food and Drug Administration
Psychopharmacologic Drugs
Advisory Committee
June 9 - 10, 2009**

► ECGs

Key Safety Conclusions

- Safety data for pediatric patients and adults described in current prescribing information**

654. In light of the fact that AstraZeneca's own April 1, 2009 SERM committee had

changed the quetiapine labels to include new warnings about the concomitant usage of quetiapine with other QT/QTc prolonging medications, the statement on June 8-9, 2009 that the "Safety data for pediatric patients and adults" concerning quetiapine's effect on the "ECG" was "described in the current prescribing information" was **false** as AstraZeneca waited eight and half months (January 15, 2010) to actually change the quetiapine labels pursuant to the Changes Being Effected regulation to include the warnings approved at the April 1, 2009 SERM meeting.

655. To reiterate, Dr. Martin Brecher testified on May 28, 2008:

7 Q. What is the core data sheet?
8 A. The core data sheet is the
9 best description of the safety profile of
10 the drug and represents the core items
11 that have to be included in every product
12 label. So it's that -- those facts about
13 the safety of the drug that must be
14 included in every label around the world.

656. For the reasons explained above, both Dr. O'Dowd's (on June 9, 2009) and Dr. Ihor Rak's (on April 8, 2009) statements made on behalf of AstraZeneca were in violation of 18 U.S.C. § 1001(1), 18 U.S.C. § 1001(2), 18 U.S.C. § 1001(3), 18 U.S.C. § 1001(4) and 21 C.F.R. 314.80(c)(2)(ii).

657. 18 U.S.C. § 1001's statutory terms are violated if someone:

1. "falsifies, conceals or covers up by any trick, scheme or device a material fact,"
2. "makes any false, fictitious or fraudulent statements or representations,"
3. "makes or uses any false writing or document knowing the same to contain any false, fictitious or fraudulent statement or entry"
4. and, for cases arising after the 1996 amendments, the item at issue was material.

658. Both Dr. O'Dowd's and Dr. Rak's statements to the FDA Advisory Committees (in April and June 2009) related to QT prolongation were both material and false under 18 U.S.C. § 1001.

659.21 C.F.R. 314.80(c)(2)(ii) states as follows:

(ii) Each periodic report is required to contain: (a) a narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification number, adverse reaction term(s), and date of submission to FDA); (b) a FDA Form 3500A (Adverse Reaction Report) for each adverse drug experience not reported under paragraph (c) (1) (i) of this section (with an index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s)); and (c) a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).

660. AstraZeneca was required under statute and regulation to disclose to the FDA Advisory Committee on April 8, 2009 and June 8-9, 2009 that a labeling change related to QT prolongation had occurred.

661. At no point before either the April 8, 2009 or the June 8, 2009 FDA Advisory Committees did AstraZeneca disclose that it had changed quetiapine's Core Data Sheet to include numerous new warnings related to the concomitant. Furthermore, at no point did AstraZeneca disclose to either the FDA Advisory Committee what **data precipitated this label change**. Lastly, AstraZeneca made affirmative statements to both the FDA Advisory Committees that there was no reason – whatsoever – to be concerned with quetiapine's effect on the QT/QTc interval.

662. In fact, AstraZeneca failed to inform the Advisory Committee that the label had been changed, the reasons for the label change or the content of the new labeling information. All of this information was in AstraZeneca's possession by April 1, 2009.

663. In Study 112, a study of quetiapine in adolescents with schizophrenia, it was

determined that Seroquel increased the QTc interval in a “dose-dependent” manner. Furthermore, the study’s findings were that “QTc prolongation was not as prominent in adults treated with quetiapine than in children and adolescents (treated with quetiapine).”

664. Curiously, in a document published by AstraZeneca titled “A 6-week, International, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia” (Study 112) the company failed to mention the finding that Seroquel increased the QTc interval in adolescents in a dose-dependent manner and stated:

The incidences of AEs of special interest that were potentially associated with QTc prolongation, neutropenia, syncope, diabetes, and suicidality were less than 5% and similar to the incidence in placebo-treated patients in all categories. Likewise, the incidence of

Clinical Study Report Synopsis Study code D1441C00112	(For national authority use only)
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clinically important shifts to low ANC levels, and to high glucose levels was similar between the quetiapine groups and the placebo group.

665. Overall, QTc prolongation is more prevalent in children taking quetiapine than it is in adults taking quetiapine.

666. To date, State Drug Utilization Boards have yet to be warned of this dangerous fact.

667. For example, in November 2010, the Texas Health and Human Services Commission published a document titled “Safety and Appropriateness of Antipsychotic Medications for Medicaid Children Under Age 16.”

668. In this document, it is clear that the dangerous effect quetiapine has on the QT

interval in children was not disclosed to the Texas Health and Human Service Commission because the document stated in relevant part:

Cardiac Adverse Effects

Antipsychotics can affect the heart by slowing down its electrical recovery or repolarization after a heartbeat. This shows up in an electrocardiogram (ECG) as lengthening of a certain part of the tracing called a QT interval. This effect, called QTc prolongation, can lead to a potentially fatal arrhythmia known as torsade de pointes. The vast majority of pediatric studies do not show any clinically significant changes in the ECG for youth on antipsychotic medications. (See Tables A-I.)

669. For example, in April 2012, the Indiana Drug Utilization Review Board published a document titled “Atypical Antipsychotic Use in Children and Adolescents.” The document stated in relevant part:

inconclusive. All of the atypical antipsychotics have some activity that results in prolongation of the QT interval and may result in cardiac dysrhythmias. How different this risk is in the young compared to adults, where most of the available data is, remains unknown. These and other areas of potential risk must all be further investigated as called for by the FDA advisory committee.

670. By stating that the relative risks of QT prolongation “in the young compared to adults...remains unknown,” this document shows that Drug Utilization Review Boards, like Indiana’s, are *unaware* of the **particularly dangerous** effect quetiapine has on the QTc interval in children and adolescents.

671. None of these results were provided to the FDA by AZ in either AZ’s May 12, 2009 Briefing Document titled “Briefing Document for Psychopharmacologic Drugs Advisory Committee” or AZ’s June 9-10, 2009 presentation to the FDA.

672. Furthermore, in its submissions to the FDA, AZ failed to notify the FDA of the April 2009 changes to the quetiapine CDS related to QT prolongation.

673. Instead, in AZ’s Briefing Document AZ omitted the dangerous QTc results found in Studies 28, 112 and 150.

674. In AZ’s June 9-10, 2009 presentation, AZ employee Dr. Liza O’Dowd made the

additional following false statement to the FDA Advisory Committee:

Summary of Safety Data—Pediatric Schizophrenia and Bipolar Mania

Liza O'Dowd, MD

**VP Clinical Development, Neuroscience
AstraZeneca Pharmaceuticals LP**

ECGs

► Safety data for pediatric patients and adults described in current prescribing information

675. In fact, the “safety data for pediatric patients and adults” was not “described in [the] current prescribing information” as AZ had changed the quetiapine label on April 1, 2009, or more than two months before, to include new information about the QT risks quetiapine posed.

676. In AZ’s June 9-10, 2009 presentation, the issue of QTc prolongation is addressed and, like the Briefing Document, omitted the dangerous QTc results found in Studies 28, 112, 149 and 150 as well as the fact that AstraZeneca had changed its quetiapine Core Data Sheet to include new warnings advising “caution” when quetiapine was used with other QT/QTc prolonging medications:

**Mean Changes in QTcF Not
Clinically Significant
Studies 112 and 149—Short-term Safety Pool**

Change from baseline	Mean change in QTcF (age 10 - 17)		
	QTP LS mean ms {SE}	Placebo LS mean ms {SE}	Difference LS mean ms {CI}
N	321	149	
To final	-0.5 (0.8)	-1.0 (1.2)	0.5 (-2.4, 3.4)
<p>▶ No increases in QTcF > 60 msec or shifts > 500 msec</p> <p>▶ No AEs of ventricular arrhythmias</p>			

I. Medicaid claim data for quetiapine prescriptions filled with drugs associated with QT/QTc prolongation

677. By May 2012, the use of quetiapine with another QTc prolonging drug was contraindicated by Texas Medicaid.

678. Texas Department of Human Services Medicaid reports from October 1, 2006 through September 30, 2007 indicate there were 2,664 methadone “Drug Drug Alerts.” Over 21% of these alerts were precipitated by a concomitant quetiapine prescription. The report reads in relevant part:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/06 and 09/30/07**

Rank	Adjudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
136	METHADONE HCL	2,664	2,144	50.97%	37	0.88%	4,206
	QUETIAPINE FUMARATE	570					
	TIZANIDINE HCL	425					
	VENLAFAXINE HCL	256					
	FLUTICASONE/SALMETEROL	200					
	PHENYTOIN SODIUM EXTENDED	172					
	RISPERIDONE	143					
	ZIPRASIDONE HCL	133					
	LEVOFLOXACIN	104					
	AZITHROMYCIN	59					
	FLUCONAZOLE	52					

679. Texas Department of Human Services Medicaid reports from October 1, 2006 through September 30, 2007 indicate that 9,261 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a risperidone prescription. Risperidone is associated with QTc prolongation. Risperidone has been shown to prolong the QTc interval. Concurrent use of risperidone with other agents that prolong the QTc interval may result in additive effects on the QTc interval. For this time period, approximately 98.13% of quetiapine prescriptions were concomitantly filled with a risperidone prescription

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/06 and 09/30/07**

Rank	Adjudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
3	RISPERIDONE	52,789	42,880	52.16%	1,535	1.87%	82,207
	QUETIAPINE FUMARATE	9,261					

680. Texas Department of Human Services Medicaid reports from October 1, 2006

through September 30, 2007 indicate that 4,589 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a ziprasidone prescription. Ziprasidone is associated with QTc prolongation. In fact, ziprasidone is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects. For this time period, approximately 97.98% of quetiapine prescriptions were concomitantly filled with a ziprasidone prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/06 and 09/30/07**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
29	ZIPRASIDONE HCL	17,512	13,581	33.26%	490	1.20%	40,827
	QUETIAPINE FUMARATE	4,589					

681. Texas Department of Human Services Medicaid reports from October 1, 2006 through September 30, 2007 indicate that 2,610 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a haloperidol prescription. Haloperidol is associated with QTc prolongation. For this time period, approximately 97.98% of quetiapine prescriptions were concomitantly filled with a risperidone microspheres prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/06 and 09/30/07**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
35	HALOPERIDOL	15,239	9,781	57.71%	343	2.02%	16,950
	BENZTROPINE MESYLATE	6,000					
	QUETIAPINE FUMARATE	2,610					

682. Texas Department of Human Services Medicaid reports from October 1, 2006

through September 30, 2007 indicate that 794 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a risperidone microspheres prescription. Risperidone microspheres is associated with QTc prolongation. For this time period, approximately 97.68% of quetiapine prescriptions were concomitantly filled with a risperidone microspheres prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/06 and 09/30/07**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
143	RISPERIDONE MICROSPHERES	2,456	1,812	38.18%	110	2.32%	4,746
	QUETIAPINE FUMARATE	794					

683. Texas Department of Human Services Medicaid reports from October 1, 2006 through September 30, 2007 indicate that 257 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a thoridazine prescription. Thoridazine is associated with QTc prolongation. In fact, thoridazine is contraindicated with other drugs known to increase the QT/QTc interval. For this time period, approximately 97.72% of quetiapine prescriptions were concomitantly filled with a thoridazine prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/06 and 09/30/07**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
171	THIORIDAZINE HCL	1,672	1,177	58.59%	45	2.28%	1,972
	QUETIAPINE FUMARATE	257					

684. Texas Department of Human Services Medicaid reports from October 1, 2006

through September 30, 2007 indicate that 80 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with an erythromycin ethysuccinate prescription. Erythromycin has an established causal association with QTc prolongation and Torsades de Pointes. For this time period, approximately 98.13% of quetiapine prescriptions were concomitantly filled with an erythromycin ethysuccinate prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/06 and 09/30/07**

Rank	Adjudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
182	ERYTHROMYCIN ETHYLSUCCINATE	1,496	1,350	8.07%	52	0.31%	16,735
	PREDNISOLONE SOD PHOSPHATE	477					
	PREDNISOLONE	167					
	FORMOTEROL FUMARATE	119					
	RISPERIDONE	101					
	QUETIAPINE FUMARATE	80					

685. Texas Department of Human Services Medicaid reports from October 1, 2007 through September 30, 2008 indicate that 536 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a budesonide/formoterol prescription. Formoterol is beta agonist and is associated with QTc prolongation. For this time period, approximately 99.03% of quetiapine prescriptions were concomitantly filled with a budesonide/formoterol prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/2007 and 9/30/2008**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
113	BUDESONIDE/FORMOTEROL FUMARATE	4,671	3,536	21.00%	164	0.97%	16,835
	AZITHROMYCIN	1,116					
	FLUTICASONE/SALMETEROL	614					
	QUETIAPINE FUMARATE	536					
	RISPERIDONE	364					
	LEVOFLOXACIN	362					
	VENLAFAXINE HCL	179					
	BUPROPION HCL	144					
	ZIPRASIDONE HCL	140					
	AMITRIPTYLINE HCL	128					
	MOXIFLOXACIN HCL	128					

686. Texas Department of Human Services Medicaid reports from October 1, 2007 through September 30, 2008 indicate that 9,105 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a risperidone prescription. Risperidone is associated with QTc prolongation. For this time period, approximately 99.1% of quetiapine prescriptions were concomitantly filled with a risperidone prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/2007 and 9/30/2008**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
4	RISPERIDONE	53,768	42,565	21.93%	1,754	0.90%	194,081
	QUETIAPINE FUMARATE	9,105					

687. Texas Department of Human Services Medicaid reports from October 1, 2007

through September 30, 2008 indicate that 21,076 risperidone, ziprasidone, paliperidone, haloperidol, levofloxacin and risperidone microspheres prescriptions implicated a drug-drug alert when filled concomitantly with an existing quetiapine prescription. Risperidone, ziprasidone, paliperidone, haloperidol, levofloxacin and risperidone microspheres are all associated with QTc prolongation. For this time period, approximately 99.43% of quetiapine prescriptions were concomitantly filled with a risperidone, ziprasidone, paliperidone, haloperidol, levofloxacin or risperidone microspheres prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/2007 and 9/30/2008**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
12	QUETIAPINE FUMARATE	39,297	33,716	17.62%	1,099	0.57%	191,399
	RISPERIDONE	9,028					
	BUPROPION HCL	7,200					
	ZIPRASIDONE HCL	4,899					
	PHENYTOIN SODIUM EXTENDED	3,962					
	TRAMADOL HCL	2,937					
	PALIPERIDONE	2,902					
	HALOPERIDOL	2,783					
	LEVOFLOXACIN	765					
	PHENYTOIN	737					
	RISPERIDONE MICROSPHERES	699					

688. Texas Department of Human Services Medicaid reports from October 1, 2007 through September 30, 2008 indicate that 2,277 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a levofloxacin prescription. Levofloxacin is associated with QTc prolongation. For this time period, approximately 99.16% of quetiapine prescriptions were concomitantly filled with a levofloxacin prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/2007 and 9/30/2008**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
13	LEVOFLOXACIN	39,127	20,667	41.56%	417	0.84%	49,726
	FLUTICASONE/SALMETEROL	4,628					
	METFORMIN HCL	2,545					
	QUETIAPINE FUMARATE	2,277					

689. Texas Department of Human Services Medicaid reports from October 1, 2007 through September 30, 2008 indicate that 3,037 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with haloperidol prescription. Haloperidol is associated with QTc prolongation. For this time period, approximately 97.7% of quetiapine prescriptions were concomitantly filled with a risperidone prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/2007 and 9/30/2008**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
38	HALOPERIDOL	16,660	10,490	63.79%	379	2.30%	16,444
	BENZTROPINE MESYLATE	6,465					
	QUETIAPINE FUMARATE	3,037					

690. Texas Department of Human Services Medicaid reports from October 1, 2007 through September 30, 2008 indicate that 617 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a fluconazole prescription. Fluconazole is associated with QTc prolongation. Fluconazole may cause prolongation of the QT/QTc interval either directly or by inhibiting the hepatic metabolism of other QT-prolonging agents like quetiapine. For this time

period, approximately 99.6% of quetiapine prescriptions were concomitantly filled with a fluconazole prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/2007 and 9/30/2008**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
48	FLUCONAZOLE	13,064	9,441	13.30%	282	0.40%	70,995
	ALPRAZOLAM	2,600					
	SIMVASTATIN	1,082					
	LEVOFLOXACIN	898					
	RISPERIDONE	635					
	ATORVASTATIN CALCIUM	618					
	QUETIAPINE FUMARATE	617					

691. Texas Department of Human Services Medicaid reports from October 1, 2007 through September 30, 2008 indicate that 524 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a haloperidol deconate prescription. Haloperidol's active drug is haloperidol. Haloperidol deconate is associated with QTc prolongation. For this time period, approximately 95.5% of quetiapine prescriptions were concomitantly filled with a haloperidol deconate prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/2007 and 9/30/2008**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
155	HALOPERIDOL DECANOATE	2,805	1,703	67.18%	114	4.50%	2,535
	BENZTROPINE MESYLATE	1,241					
	QUETIAPINE FUMARATE	524					

692. Texas Department of Human Services Medicaid reports from October 1, 2007

through September 30, 2008 indicate there were 2,847 methadone "Drug Drug Alerts." Methadone is associated with QTc prolongation. Over 21% of these alerts were precipitated by a concomitant quetiapine prescription. The report reads in relevant part:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/2007 and 9/30/2008**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
152	METHADONE HCL	2,847	2,260	21.07%	43	0.40%	10,726
	QUETIAPINE FUMARATE	599					
	TIZANIDINE HCL	443					
	VENLAFAXINE HCL		322				
	FLUTICASONE/SALMETEROL		253				
	PHENYTOIN SODIUM EXTENDED		174				
	RISPERIDONE		144				
	LEVOFLOXACIN		119				
	ZIPRASIDONE HCL		85				
	FLUCONAZOLE		69				
	AZITHROMYCIN		68				

693. Texas Department of Human Services Medicaid reports from October 1, 2007 through September 30, 2008 indicate that 282 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a clarithromycin prescription. Clarithromycin has an established causal association with QT prolongation and Torsades de Pointes. For this time period, approximately 99.64% of quetiapine prescriptions were concomitantly filled with a clarithromycin prescription:

**Texas Department of Human Services
Medicaid FED_YTD DUR Report for Top 200 Drugs DD
For Claims Processed Between 10/01/2007 and 9/30/2008**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
176	CLARITHROMYCIN	2,179	1,684	9.78%	62	0.36%	17,215
	SIMVASTATIN	299					
	QUETIAPINE FUMARATE	282					

694. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 9,448 risperidone prescriptions implicated a drug-drug alert when filled concomitantly with a quetiapine prescription. Risperidone is associated with QTc prolongation. For this time period, approximately 98.68% of risperidone prescriptions were concomitantly filled with a quetiapine prescription:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
5	RISPERIDONE	55,482	43,519	21.81%	2,639	1.32%	199,526
	QUETIAPINE FUMARATE	9,448					

695. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 22,694 risperidone, ziprasidone, paliperidone, haloperidol, levofloxacin, risperidone microspheres and budesonide/formoterol prescriptions implicated a drug-drug alert when filled concomitantly with an existing quetiapine prescription. Risperidone, ziprasidone, paliperidone, haloperidol, risperidone microspheres, levofloxacin and budesonide/formoterol are all associated with QTc prolongation. For this time period, approximately 99.31% of quetiapine prescriptions were concomitantly filled with a risperidone

ziprasidone, paliperidone, haloperidol, risperidone microspheres, levofloxacin or budesonide/formoterol prescription:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
12	QUETIAPINE FUMARATE	41,142	35,072	17.95%	1,353	0.69%	195,391
	RISPERIDONE	8,795					
	BUPROPION HCL	6,702					
	ZIPRASIDONE HCL	4,603					
	PHENYTOIN SODIUM EXTENDED	4,055					
	PALIPERIDONE	3,493					
	TRAMADOL HCL	3,481					
	HALOPERIDOL	2,878					
	BUDESONIDE/FORMOTEROL FUMARATE	1,096					
	RISPERIDONE MICROSPHERES	1,076					
	LEVOFLOXACIN	753					

696. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 2,121 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a levofloxacin prescription. Levofloxacin is associated with QTc prolongation. For this time period, approximately 99.08% of quetiapine prescriptions were concomitantly filled with a levofloxacin prescription:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
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15	LEVOFLOXACIN	37,146	19,706	41.98%	432	0.92%	46,937
	FLUTICASONE/SALMETEROL	5,312					
	METFORMIN HCL	2,676					
	PREDNISONE	2,401					
	QUETIAPINE FUMARATE	2,121					

697. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 4,508 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a ziprasidone prescription. Ziprasidone is associated with QTc prolongation. For this time period, approximately 98.81% of quetiapine prescriptions were concomitantly filled with a ziprasidone prescription:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
35	ZIPRASIDONE HCL	19,650	14,966	28.71%	622	1.19%	52,131
	QUETIAPINE FUMARATE	4,508					

698. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 3,038 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a haloperidol prescription. Haloperidol is associated with QTc prolongation. For this time period, approximately 97.1% of quetiapine prescriptions were concomitantly filled with a haloperidol prescription:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
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37	HALOPERIDOL	18,328	11,398	65.21%	507	2.90%	17,478
	BENZTROPINE MESYLATE	7,479					
	QUETIAPINE FUMARATE	3,038					

699. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 1,524 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a fluconazole prescription. Fluconazole is associated with QTc prolongation. For this time period, approximately 99.54% of quetiapine prescriptions were concomitantly filled with a fluconazole prescription:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
53	FLUCONAZOLE	14,582	10,437	14.04%	343	0.46%	74,315
	ALPRAZOLAM		2,642				
	QUETIAPINE FUMARATE		1,524				

700. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 230 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with an amiodarone prescription. Amiodarone is associated with QTc prolongation. For this time period, approximately 96.43% of quetiapine prescriptions were concomitantly filled with an amiodarone prescription:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
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102	AMIODARONE HCL	5,900	3,251	65.10%	179	3.57%	5,009
	WARFARIN SODIUM	1,304					
	SIMVASTATIN	820					
	DIGOXIN	770					
	METOPROLOL TARTRATE	593					
	METOPROLOL SUCCINATE	455					
	DILTIAZEM HCL	235					
	QUETIAPINE FUMARATE	230					

701. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 1,331 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a risperidone microspheres prescription. Risperidone microspheres is associated with QTc prolongation. For this time period, approximately 98.4% of quetiapine prescriptions were concomitantly filled with a risperidone microspheres prescription:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Adjudicated Claims for Drug
118	RISPERIDONE MICROSPHERES	4,793	3,478	35.22%	158	1.60%	9,875
	QUETIAPINE FUMARATE	1,331					

702. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 366 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a moxifloxacin HCL prescription. Moxifloxacin HCL is associated with QTc prolongation. In fact, in 1999 an FDA Medical Review Officer stated that, “[m]oxifloxacin clearly prolongs QTc intervals in a concentration-related manner and, as a result, put patients at risk for developing malignant arrhythmias.” For this time period, approximately 99.96% of quetiapine prescriptions were concomitantly filled with a moxifloxacin HCL prescription:

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Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
127	MOXIFLOXACIN HCL	4,458	2,553	1.63%	56	0.04%	156,183
	FLUTICASONE/SALMETEROL	1,208					
	PREDNISONE	494					
	QUETIAPINE FUMARATE	366					

703. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 608 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a haloperidol deconate prescription. Haloperidol deconate is associated with QTc prolongation. For this time period, approximately 94.47% of quetiapine prescriptions were concomitantly filled with a haloperidol deconate prescription:

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Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
146	HALOPERIDOL DECANOATE	3,341	1,960	69.93%	141	5.03%	2,803
	BENZTROPINE MESYLATE	1,408					
	QUETIAPINE FUMARATE	608					

704. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate that 273 quetiapine prescriptions implicated a drug-drug alert when filled concomitantly with a clarithromycin. Clarithromycin is associated with QTc prolongation. For this time period, approximately 99.63% of quetiapine prescriptions were concomitantly filled with clarithromycin prescription:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
176	CLARITHROMYCIN	2,346	1,852	8.18%	84	0.37%	22,633
	SIMVASTATIN	319					
	QUETIAPINE FUMARATE	273					

705. Texas Department of Human Services Medicaid reports from October 1, 2008 through September 30, 2009 indicate there were 3,056 methadone “Drug Drug Alerts.” Methadone is associated with QTc prolongation. Nearly 25% of those alerts were precipitated by a concomitant quetiapine prescription. The report reads in relevant part:

**Texas Health and Human Services Commission
Medicaid FED_YTD DUR Report for Top 200 Drugs for Alert DD
For Claims Processed Between 10/01/2008 and 9/30/2009**

Rank	Ajudicated Drug History Drug	DD Alert Occurrences	DD Claims for Drug	%DD Claims for Drug	DD Claims Reversed	%DD Claims Reversed	Total Ajudicated Claims for Drug
153	METHADONE HCL	3,056	2,463	21.40%	48	0.42%	11,511
	QUETIAPINE FUMARATE	736					

706. From October 2006 through September 2009, Texas Medicaid beneficiaries had over 103,091 quetiapine prescriptions filled concomitantly with drugs known to prolong the QTc interval (including, but not limited to, methadone, budesonide/formoterol, risperidone, risperidone microspheres, ziprasidone, haloperidol, haloperidol deconate, thioridazine, erythromycin ethysuccinate, levofloxacin, fluconazole, clarithromycin, paliperidone, amiodarone and moxifloxacin HCL). Each of these quetiapine prescriptions are now subject to the prior authorization process where the physician must justify why she/he wants to use two

contraindicated drugs together. These prescriptions will not be paid for until Texas Medicaid approves the prior authorization request and, consequently, payment for the drugs.

707. From January 2006 through December 2009, approximately 18% of quetiapine prescriptions paid for by Texas Medicaid, or approximately 125,000 out of a total 689,359 quetiapine prescriptions during this time period, were filled concomitantly with drugs known to increase the QT/QTc interval.

708. For this same time period in Florida, approximately 35% of quetiapine prescriptions (186,785) paid for by Florida Medicaid were filled concomitantly with drugs known to increase the QT/QTc interval.

709. Furthermore, the use quetiapine with beta-agonists (i.e., levabuterol, albuterol and formoterol) is now contraindicated because the use of quetiapine with any of these agents “may potentiate” adverse effects on the cardiovascular system.

710. The warning label for each beta-agonist has included the following warning since at least September 2001:

Beta agonists **should be used with extreme caution** in patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or **drugs known to increase the QTc interval** because the action of the adrenergic agonists on the cardiovascular system **may be potentiated by these agents**. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias. (emphasis added).

711. From September 2010 through August 2011, Texas Medicaid paid for approximately 852,249 separate claims for beta-agonists.

712. From approximately January 2006 through December 2009 the State of Texas paid approximately \$42,915,375.90 for quetiapine prescriptions filled concomitantly with drugs known to increase the QTc interval.

713. From January 2006 through December 2009 the State of California paid anywhere

from \$90,151,833.174 (or 18% of the total amount spent on quetiapine by California) to \$175,295,329.30 (or 35% of the total amount spent on quetiapine by California) for quetiapine prescriptions filled with other drugs known to prolong the QT/QTc interval.

714. In California, from January 2006 through December 2009 the state of California paid for 272,751 prescriptions (or 18% of the total number of quetiapine prescriptions paid for by California) to 530,350 (or 35% of the total number of quetiapine prescriptions paid for by California) for quetiapine prescriptions filled with other drugs known to prolong the QT/QTc interval.

715. In Illinois, from January 2006 through December 2009 the State of Illinois paid anywhere from \$25,172,712 (or 18% of the total amount spent on quetiapine by Illinois) to \$48,946,940 (or 35% of the total amount spent on quetiapine by Illinois) for quetiapine prescriptions filled with other drugs known to prolong the QT/QTc interval.

716. The State of Illinois paid for 98,213 prescriptions (or 18% of the total number of quetiapine prescriptions paid for by Illinois) to 190,970 (or 35% of the total number of quetiapine prescriptions paid for by Illinois) for quetiapine prescriptions filled with other drugs known to prolong the QT/QTc interval.

717. As of May 2012, Texas Medicaid directs that the concomitant use of quetiapine with any drug that causes prolongation of the QTc interval is **contraindicated**.

718. Numerous State Drug Utilization Review Boards have taken steps to ensure that quetiapine is not filled concomitantly with other QT/QTc prolonging agents.

719. For example, from October 2010 through September 2011, the State of Massachusetts refused to pay for 6.7% of all quetiapine prescriptions (12,996/192,894) because of a QT/QTc drug/drug interaction (a "Level 1" drug/drug interaction).

720. For example, from October 2011 through September 2012, the State of Massachusetts refused to pay for 12.6% of all quetiapine prescriptions (24,480/193,940) because of a QT/QTc drug/drug interaction (a “Level 1” drug/drug interaction) precipitated by the June 2011 FDA imposed label change.

721. For example, from October 2011 through September 2012, the State of Nevada refused to pay for 15% of all quetiapine prescriptions because of a QT/QTc drug/drug interaction. The State of Nevada estimated that it saved \$18,437,243 (or 42% of all its Drug Utilization Review savings for the year) by this intervention (a “Level 1” drug/drug interaction).

722. For example, from October 2011 through September 2012, the State of Tennessee saved \$678,718.22 by refusing to pay for the concomitant prescriptions of quetiapine with another QT/QTc prolonging drug (a “Level 1” drug/drug interaction).

723. For example, from October 2011 through September 2012, the State of Montana rejected 8.23% of all quetiapine prescriptions because of a QT/QTc drug/drug interaction (a “Level 1” drug/drug interaction).

724. For example, from October 2011 through September 2012, the State of Nebraska identified – and rejected – 21,782 quetiapine prescriptions because of QT/QTc drug/drug interaction (a “Level 1” drug/drug interaction).

725. For example, from October 2011 through September 2012, the State of Vermont saved \$94,473.22 by rejecting quetiapine prescriptions because of a QT/QTc drug/drug interaction (a “Level 1” drug/drug interaction).

726. For example, from October 2011 through September 2012, the State of Mississippi rejected 10.36% of all quetiapine prescriptions because of a QT/QTc drug/drug interaction (a “Level 1” drug/drug interaction).

727. For example, from October 2011 through September 2012, the State of Idaho rejected 8.7% of all quetiapine prescriptions because of a QT/QTc drug/drug interaction (a “Level 1” drug/drug interaction).

728. Seroquel and Seroquel XR’s total Medicaid sales from 1997 through 2010 totaled approximately \$8.65 billion.

729. If AstraZeneca had complied with federal law State Medicaid agencies and the federal government would have saved anywhere from \$582 million (predicated on the Massachusetts reject rate of 6.7% of all Medicaid quetiapine purchases and the “caution” label change implemented by AstraZeneca eight months after the label was changed internally) to \$1.65 billion (predicated on the Nevada reject rate of 15% of all Medicaid quetiapine purchases and the “should be avoided” FDA-mandated label change).

730. According to a March 2003 study by the Texas Comptroller, when a pharmacist in Texas is filling Texas Medicaid prescriptions and identifies a “significant problem” (such as the concomitant use of two contraindicated drugs), the pharmacist must take steps to avoid or resolve the problem including contacting the prescribing physician. The report reads in relevant part:

Drug Utilization Review

In addition to the regional pharmacists, the VDP performs prospective drug use review through the online pharmacy claims adjudication system. This was implemented in September 1993, to comply with the Omnibus Budget Reconciliation Act of 1990

(OBRA '90) that requires pharmacists to conduct prospective drug use reviews and to provide patient counseling for all Medicaid patients. The OBRA '90 drug review requires pharmacists to review a patient's medication record (specific demographic, allergy and past drug information maintained on each patient) and the drug order prior to dispensing a new or refill medication. The pharmacist must identify problems such as:

- inappropriate drug use;
- therapeutic duplication;
- drug-disease contraindications;
- drug-drug interaction;
- incorrect drug dosage or duration of drug treatment;
- drug-allergy interactions; and
- clinical abuse or misuse.

If the pharmacist identifies a significant problem, the pharmacist must take steps to avoid or resolve the problem including consulting the prescribing physician.¹¹

731. In April 2012, Thomas M. Suehs, Executive Commissioner for the Texas Health and Human Services Commission issued a "Request for Proposal ("RFP") for Medicaid Drug Use Review." In the RFP, Mr. Suehs reaffirmed the requirement that when pharmacists identify a significant problem (such as the concomitant usage of two contraindicated medications), the pharmacist must take steps to avoid or resolve the problem including consulting the prescribing physician. The RFP reads in relevant part:

The OBRA '90 drug review requires pharmacists to review each Medicaid patient's medication record (including specific demographic, allergy and past drug information) and the drug order before dispensing a new or refill medication. The pharmacist must identify problems such as:

- inappropriate drug use;
- therapeutic duplication;
- drug-disease contraindications;
- drug interactions;
- incorrect drug dosage or duration of drug treatment;
- drug-allergy interactions; and
- clinical abuse or misuse.

If the pharmacist identifies a significant problem, he or she must take steps to avoid or resolve the problem, including consulting the prescribing physician.

732. In Texas, when an attempt is made to fill one drug (quetiapine) with another drug

with which it is contraindicated (e.g., a QTc interval-prolonging drug) the claim rejects with a “Code 88-DUR Reject Error.”

733. The pharmacist can only override the rejection if he/she determines “that the physician understands the risks to be acceptable, and appropriate monitoring measures are undertaken.”

734. Texas Medicaid states that the “appropriate monitoring measures” for patients taking quetiapine with other QTc interval-prolonging drugs are to “closely monitor cardiac function” during the concomitant drug therapy and “discontinue (concomitant) therapy in patients with QTc measurements > 500 msec.”

735. Prior to June 2011, physicians, pharmacists and Texas Medicaid were unaware of the dangers posed by the concomitant prescription of quetiapine with another QTc prolonging medication.

736. Accordingly, prior to June 2011, physicians prescribed, pharmacists filled and Texas Medicaid paid for these medications (quetiapine with another QTc prolonging medication) with none of the necessary “appropriate monitoring measures” now required in Texas when such drugs are filled together.

737. AstraZeneca’s 2006 Corporate Responsibility Report represented that “[i]f information suggests a change is needed in a [drug’s] benefit/risk profile, the actions we can take include conducting further clinical trials, modifying the prescribing information, and communicating with healthcare professionals and others who need to know of the change.”

738. Despite this representation, at no point prior to January 2010 was there any warning in Seroquel’s prescribing information about the lethal risks posed by the concomitant use of quetiapine with drugs known to increase the QT/QTc interval.

739. To the contrary, AstraZeneca repeatedly told State Drug Utilization Boards that Seroquel had no effect on the QT/QTc interval.

740. If physicians knew of Seroquel's true effect on the QT/QTc interval, concomitant prescriptions of Seroquel with other QT/QTc prolonging drugs would never have been written. And, if pharmacists knew of Seroquel's true effect on the QT/QTc interval, the federal and state systems in place to protect Medicaid and Medicare Part D beneficiaries from dangerous drug interactions would have led pharmacists to reject the claims that were subsequently paid for by the government. Instead, the inadequate drug interaction alert was predicated on **false and misleading information disseminated by AstraZeneca concerning Seroquel's true effect on prolonging the QTc interval.**

741. State Medicaid Drug Utilization Review Boards would have required that a physician obtain a "prior authorization," which it would have authority to approve or deny the now contraindicated use of quetiapine with QT/QTc prolonging drugs prior to the payment for and filling of the two prescriptions.

742. Alternatively, pharmacists, who also materially relied on the Seroquel labels, would have refused to fill the quetiapine prescriptions with QT/QTc prolonging drugs out of safety concerns posed by the concomitant usage of such drugs.

J. Reasonable evidence of quetiapine's association with opioid deaths

743. High doses of opioids like oxycodone are associated with longer QTc intervals.

744. An analysis of Virginia's drug related deaths from 2006-2009 showed that quetiapine was five times more likely to present in "drug related deaths" than olanzapine (Zyprexa), more than twenty times more likely to be present in "drug related deaths" than

cloazpine (Clozaril) and more than one hundred times more likely to be present in “drug related deaths” than risperidone (Risperdal).

745. Wayne County, Michigan medical examiner reports indicate that from 2007-2011 105 people died with hydrocodone and quetiapine in their system and 28 people died with oxycodone and quetiapine in their system.

746. 2006 New Mexico medical examiner reports indicate that 30 people died during 2007 with either quetiapine or its metabolites in their system. The antipsychotic with the next largest number was olanzapine with 6.

747. 2007 New Mexico medical examiner reports indicate that 48 people died during 2007 with either quetiapine or its metabolites in their system. The antipsychotic with the next largest number was olanzapine with 4.

K. Federal law governing the content of drug labeling

748. There are numerous regulations governing the content of drug labeling. One regulation, 21 C.F.R. 201.57(e), is especially relevant to Plaintiff-Relator’s allegations. The regulation imposes an affirmative duty on a manufacturer to revise a drug’s labeling once there is a “reasonable association of a serious hazard with a drug.”

749. The regulation reads in its entirety:

Warnings. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the Indications and Usage section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may

also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the Adverse Reactions section of the labeling. (emphasis added).

750. In April 2009, AstraZeneca changed its “Core Data Sheet” to include a new warning about the dangers posed by the concomitant use of quetiapine with other QT/QTc prolongation medications.

751. Dr. Martin Brecher, a medical science director at AstraZeneca, testified that that Core Data Sheet is “the best description of the safety profile of the drug and represents the core items that have to be included in every product label. So it’s that – those facts about the safety of the drug that must be included in every label around the world.”

752. Despite that fact that AstraZeneca’s Safety Evaluation Review Meeting changed the quetiapine “Core Data Sheet” to include a new warning about the dangers posed by the concomitant use of quetiapine with QT/QTc prolonging medications on April 1, 2009, AZ nevertheless:

- Concealed this information from the April 8, 2009 FDA Advisory Committee that was specifically called to address the safety issues related to the use of Seroquel XR.
- Concealed this information from the June 8-9, 2009 FDA Pediatric Advisory Committee that was specifically called to address the safety issues related to the use of Seroquel in pediatric patients.
- Delayed the addition of the new QT/QTc warning to the Seroquel and Seroquel XR United States labels for eight and half months despite the fact that federal law requires that such a label change be done “**as soon as there is reasonable evidence** of a serious hazard with a drug; a causal relationship need not have been proved.”

753. As previously stated, in its 2006 Corporate Responsibility Report, AstraZeneca states that if information “**suggests** that a change is needed in a benefit/risk profile, the actions we can take can include conducting further clinical trials, modifying the prescribing information,

and communicating with healthcare professionals and others that need to know of the change.”

The document reads in relevant part:

AFTER LAUNCH

Understanding how our medicines are working on a day-to-day basis is also crucial to meeting our commitment to patient safety. After launch, we monitor all our medicines for any side effects not identified during the development process. Clinical trials, although extensive, cannot replicate the complete range of patient circumstances that exist among much larger and more diverse patient populations. Rare side effects can often only be identified after a medicine has been launched and used in far greater numbers of patients and over longer periods of time. If information received suggests a change is needed in a benefit/risk profile, the actions we take can include conducting further clinical trials, modifying the prescribing information, and communicating with healthcare professionals and others who need to know of the change. In certain situations, it may be appropriate to stop an ongoing clinical trial or withdraw a product from the market.

754. AZ had full knowledge from at least 1997 onwards that the use of quetiapine causes clinically significant increases in the QTc interval and that there was a “reasonable evidence of an association of serious hazard” when quetiapine is taken concomitantly with another drug that causes QTc prolongation.

755. The concomitant use of two QTc prolonging drugs represents both a clear “potential safety hazard” and “serious hazard” anticipated by 21 C.F.R. 201.57(e).

756. Nevertheless, the labeling for both Seroquel and Seroquel XR did not contain any safety information related to the dangers associated with taking quetiapine with other QTc prolonging drugs as required under 21 C.F.R. 201.57(e) until January 2010.

757. Only when the FDA **required** a label change did the quetiapine label warn that the use of quetiapine should be “avoided” with drugs known to cause increases in the QTc interval until June 2011.

758. 21 C.F.R. 201.57(e) is not the only regulation that imposes an affirmative duty on AstraZeneca to strengthen both Seroquel and Seroquel XR’s labeling. Known as the “Changes Being Effectuated” regulation, 21 C.F.R. §314.70(c)(6)(iii) allows drug manufacturers to strengthen safety language without FDA approval.

759. 21 C.F.R. §314.70(c)(6)(iii) reads in its entirety:

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a Supplement for a change.

These changes include, but are not limited to: (i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess; (ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another; **(iii) Changes in the labeling to accomplish any of the following: (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction; (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage; (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;** (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or (E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

760. The Supreme Court in *Wyeth v. Levine* emphasized that the “Changes Being Effectuated” regulation:

“provides that if a manufacturer is changing a label to “add or strengthen a contraindication, warning, precaution or adverse reaction” or to “add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product,” it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval.” §§314.70(c)(6)(iii)(A),(C).

761. In May 2007, AstraZeneca submitted a new drug application under the “Changes Being Effected” provision that strengthened the warnings in Seroquel’s label. On July 30, 2007, the FDA accepted these changes. The letter from the FDA to AstraZeneca accepting these changes reads in relevant part:

This new drug application, submitted under “Changes Being Effected” provides for the following revisions to labeling:

- 1. Revisions to the Black Box entitled Suicidality and Antidepressant Drugs at the beginning of the prescriber labeling.**
- 2. Revisions to the WARNINGS–Clinical Worsening and Suicide Risk section.**
- 3. Revisions to the PRECAUTIONS–Information for Patients section.**
- 4. Revisions to the MEDICATION GUIDE.**

762. Consequently, AstraZeneca unilaterally strengthened Seroquel’s label to include a black box warning concerning the risks of using Seroquel and an increased risk of suicidality. Furthermore, AstraZeneca amended Seroquel’s Warning, Precautions and Medication Guide sections. However, AstraZeneca failed to amend Seroquel’s label to include any information from the Uehlinger study or about Seroquel’s known effects on prolonging the QTc interval.

763. As addressed *supra*, AstraZeneca implemented a “Changes Being Effected” label change in June 2007 within just two weeks after convening a Safety Evaluation and Review Meeting. The “Changes Being Effected” label change related to QT/QTc prolongation that occurred in January 2010 occurred eight and half months after convening a Safety Evaluation and Review Meeting.

764. 42 U.S.C. § 1395y(a)(1)(A) prohibits Medicare payments for treatments that are not “reasonable and necessary.”

765. In general, Medicare coverage and payment is contingent upon a determination that: a service is in a covered benefit category; a service is not specifically excluded from Medicare coverage by the Act; and the item or service is “reasonable and necessary” for the diagnosis or

treatment of an illness or injury, to improve functioning of a malformed body member, or is a covered preventive service.

766. By definition, a drug that is introduced into interstate commerce without the requisite instructions for safe use meets neither the “reasonable” nor the “necessary” standard required under 42 U.S.C. § 1395y(a)(1)(A).

767. In fact, 42 U.S.C. 1396r-8(g)(1)(A) states that the goal State Medicaid Drug Utilization Review Programs is to “identify and reduce...inappropriate or medically unnecessary care.” 42 U.S.C. 1396r-8(g)(1)(A) reads:

“The program shall be designed to educate physicians and pharmacists to identify and reduce the frequency of patterns of fraud, abuse, gross overuse, or **inappropriate or medically unnecessary care**, among physicians, pharmacists, and patients, or associated with specific drugs or groups of drugs, as well as potential and actual severe adverse reactions to drugs including education on therapeutic appropriateness, overutilization and underutilization, appropriate use of generic products, therapeutic duplication, drug-disease contraindications, **drug-drug interactions**, incorrect drug dosage or duration of drug treatment, drug-allergy interactions, and clinical abuse/misuse. (emphasis added).

768. Despite knowing that the use of Seroquel and Seroquel XR were inherently dangerous with a warning advising – at the very least – “caution” when used with QT/QTc prolonging medications, AstraZeneca nevertheless failed to amend the label to include such a warning prior to January 15, 2010.

769. AstraZeneca’s failure to include a warning about the concomitant use of quetiapine with other QT/QTc prolonging medications until January 15, 2010 corrupted the drug utilization review programs of State Medicaid programs. In effect, if there were no warnings about the dangers posed by the concomitant usage of quetiapine with QT/QTc prolonging medications, State Medicaid programs could not act to ensure such concomitant prescriptions were appropriate or medically necessary.

770. AstraZeneca’s failure to include a warning about the concomitant use of

quetiapine with other QT/QTc prolonging medications until January 15, 2010 corrupted the drug utilization review programs of the Medicare Part D program. In effect, if there were no warnings about the dangers posed by the concomitant usage of quetiapine with QT/QTc prolonging medications, the Medicare Part D program could not act to ensure such concomitant prescriptions were appropriate or medically necessary.

771. Thus, AZ, by failing to amend the quetiapine label when it had reasonable evidence of an association of a serious hazard when quetiapine is used with QT/QTc prolonging medications AZ caused prescriptions of quetiapine (Seroquel or Seroquel XR) that were prescribed concomitantly with QT/QTc prolonging medications to be submitted for payment by Medicare that were, by definition, not “reasonable and necessary” as there was insufficient warnings in the quetiapine labels to help ensure safe usage.

772. AstraZeneca had reasonable evidence of a serious hazard when quetiapine is used with QT/QTc prolonging medications in **January 2003** when an AstraZeneca funded study **excluded patients from participating in a study who had a QTc \geq 450 ms or who were taking QTc prolonging medications.**

773. AstraZeneca had reasonable evidence of a serious hazard when quetiapine is used with QT/QTc prolonging medications in **April 2004** when it excluded patients from participating in a study who had a QTc >450 ms for the AZ stated reason so as **“not to jeopardize patient safety.”**

774. AstraZeneca had reasonable evidence of a serious hazard when quetiapine is used with QT/QTc prolonging medications when in **February 2006** the European Union imposed a warning that “caution” should be used when quetiapine is used with QT/QTc prolonging medications.

775. AstraZeneca had reasonable evidence of a serious hazard when quetiapine is used with QT/QTc prolonging medications in **January 2007** when FDA required a warning that the use of paliperidone (“Invega”) “should be avoided” with QT/QTc prolonging medications on the paliperidone label in light of a head-to-head study in December 2006 showed that quetiapine had a greater effect on the QTc interval than did paliperidone. The January 2007 Invega label reads in relevant part:

QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

776. AstraZeneca’s knowledge of the results of the head-to-head study with paliperidone and quetiapine (that showed that quetiapine had a greater effect on the QTc interval than did paliperidone) and FDA’s decision about paliperidone’s QT/QTc warning constituted reasonable evidence of a serious hazard when quetiapine is used with QT/QTc prolonging medications thus triggering AstraZeneca’s duty to amend its quetiapine labels.

777. AstraZeneca had reasonable evidence of a serious hazard when quetiapine is used with QT/QTc prolonging medications in **August 2009** when FDA determined that asenapine (“Saphris”) “has a roughly comparable effect on QT prolongation” as did quetiapine. FDA required that the asenapine label should contain a warning that the use of asenapine with QT/QTc prolonging medications “should be avoided.” The August 2009 Saphris label reads in relevant part:

The use of SAPHRIS should be avoided in combination with other drugs known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin). SAPHRIS should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including bradycardia; hypokalemia or hypomagnesemia; and presence of congenital prolongation of the QT interval.

778. AstraZeneca's knowledge of the results of the head-to-head study with asenapine and quetiapine and FDA's decision about asenapine's QT/QTc warning constituted reasonable evidence of a serious hazard when quetiapine is used with QT/QTc prolonging medications thus triggering AstraZeneca's duty to amend its quetiapine labels.

779. On May 28, 2008, AstraZeneca's Dr. Martin Brecher defined the Core Data Sheet as the "best description of the safety profile of the drug and represents the core items that have to be included in every product label...So it's that – those facts about the safety a drug that **must be included in every label around the world.**" (emphasis added).

780. As further described *supra*, AstraZeneca **itself** changed the Core Data Sheet on April 1, 2009 for quetiapine to contain a warning to advise caution when quetiapine is used with QT/QTc prolonging medications.

781. Yet, instead of changing the label immediately or shortly thereafter, AstraZeneca waited **eight and half months** before unilaterally changing the label to include the "caution" warning with QT/QTc prolonging medications pursuant to the Changes Being Effected regulation.

782. Additionally, in September 2007 AstraZeneca implemented changes in Seroquel's

label pursuant to the “Changes Being Effectuated” provision. The FDA referenced these changes in its January 2008 correspondence with AstraZeneca. The letter from the FDA to AstraZeneca reads in relevant part:

These new drug applications, submitted under “Changes Being Effectuated” provide for the following revisions to labeling:

S-031

- This submission provides for changes in the Laboratory Changes under the section of ADVERSE REACTIONS and OVERDOSE sections. Additionally, cardiomyopathy and myocarditis have also been added to the ADVERSE REACTION section.

S-039

1. Revisions to the PRECAUTIONS – Leukopenia, Neutropenia, and Agranulocytosis section.
2. Revisions to the PRECAUTIONS – Information for Patients section.
3. Revisions to the Laboratory Tests section.
4. Revisions to the Adverse Events – Laboratory Changes section.
5. Revisions to the Post-Marketing Experience section.

783. Consequently, in September 2007 AstraZeneca unilaterally strengthened Seroquel’s label to include new information about the risk of leukopenia, neutropenia and agranulocytosis associated with Seroquel. Furthermore, AstraZeneca amended the label with new information about “Information for Patients,” “Laboratory Tests,” “Adverse Events-Laboratory Changes” and “Post-Marketing Experience” associated with Seroquel. However, AstraZeneca failed to amend Seroquel’s label to include any information from the Uehlinger study or Seroquel’s known and dangerous effect of prolonging the QTc interval or to provide any warning concerning the concomitant use of quetiapine with another drug known to increase the QTc interval.

784. Furthermore, despite the abundance of scientific data, multiple warnings in Europe related to the dangers of using quetiapine with other QTc prolonging drugs, and abundance of adverse event reports, at no point prior to January 2010 were physicians,

pharmacists, and State Drug Utilization Boards warned about the dangers posed to Medicaid beneficiaries when quetiapine is used with other QTc prolonging drugs.

785. Writing for the majority in the Supreme Court case *Wyeth v. Levine*, Justice Stevens opined on the issue of whether a manufacturer has an affirmative duty to amend a drug's label once new safety information is available:

Wyeth's cramped reading of the CBE regulation and its broad reading of the FDCA's misbranding and unauthorized distribution provisions are premised on a more fundamental misunderstanding. Wyeth suggests that the FDA, rather than the manufacturer, bears primary responsibility for drug labeling. Yet through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market. See, e.g., 21 CFR §201.80(e) (requiring a manufacturer to revise its label "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug"); §314.80(b) (placing responsibility for post-marketing surveillance on the manufacturer); 73 Fed. Reg. 49605 ("Manufacturers continue to have a responsibility under Federal law . . . to maintain their labeling and update the labeling with new safety information").

786. Furthermore, Justice Stevens addressed the issue of whether manufacturer's have "superior access to information about their drugs" vis-à-vis the FDA stating:

In keeping with Congress' decision not to pre-empt common-law tort suits, it appears that the FDA traditionally regarded state law as a complementary form of drug regulation. The FDA has limited resources to monitor the 11,000 drugs on the market,¹¹ and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.

787. In a June 21, 2010 letter to a physician who submitted a request for information about the use of Seroquel with methadone, AstraZeneca **explicitly agreed** with the Court stating in relevant part:

Manufacturers have the most complete data regarding the metabolism of their respective drugs and may be an additional source of information regarding potential drug interactions with quetiapine. In addition, Bertz and Granneman⁵ have published a review article that lists the various narcotic analgesics metabolized via cytochrome P450 isoenzymes and whether or not they are hepatic inducers or inhibitors. The article points out that alfentanil, fentanyl, and methadone are primarily metabolized by CYP 3A4.

788. Separately, on September 15, 2010, AstraZeneca sent another letter to a separate physician who requested information about the safety of using methadone with quetiapine.

789. Neither the September 15, 2010 letter nor the June 21, 2010 letter informed the physicians that, according to a March 2010 MEB report, **“quetiapine has shown some potential to increase QTc next to methadone,** by which combination could lead to a potentially dangerous situation as is currently warned for in section 4.5 of the SPC (Summary of Product Characteristics). In addition, **as many of the reported cases had a fatal outcome,** the MAH (Market Authorization Holder – AstraZeneca) should continue to monitor the interaction closely.”

790. Neither the September 15, 2010 letter nor the June 21, 2010 letter informed the physicians that AstraZeneca had changed the Seroquel and Seroquel XR labels to include a new warning advising “caution” when either drug was used with another QT/QTc prolonging medication like methadone.

791. Like the FDA, physicians, pharmacists, and State Drug Utilization Review Boards have limited resources to monitor the thousands of drugs for which they have responsibility.

792. Accordingly, Drug Utilization Review Boards are **especially reliant** on the

information provided from the manufacturers of drug products (including, but not limited to, manufacturers' labels) to make **fully informed** decisions on drug-drug interactions that affect the lives of Medicaid beneficiaries.

793. Accordingly, pharmacists are **especially reliant** on the information provided from the manufacturers of drug products (including, but not limited to, manufacturers' labels) to make **fully informed** decisions on drug-drug interactions that affect the lives of Medicaid beneficiaries.

794. Consequently, a manufacturer should, without FDA approval, amend a drug's labeling to add or strengthen a contraindication, warning, precaution or adverse reaction, to add or strengthen a statement about drug abuse, dependence, psychological effect or overdosage or to add or strengthen an instruction about dosage and administration intended to increase safe use of the drug, including drug interactions, as soon as there is **reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.**

795. The Court noted in *Wyeth*:

"As the FDA explained in the notice of the final rule, "newly acquired information" is not limited to new data, but also encompasses "new analyses of previously submitted data."

796. One of the reasons why AsraZeneca belatedly amended its label on January 15, 2010 pursuant to the CBE regulation to include a warning advising "caution" when quetiapine is used with QT/QTc prolonging medications were due to reports of QT prolongation in patients who had taken an overdose of quetiapine.

797. Yet the Dutch regulatory authority identified this danger in January 2003 and, thus, reports of QT prolongation in quetiapine overdose. Consequently, the danger of QT prolongation in quetiapine overdose was not "new."

798. European regulators reviewed the information related to quetiapine and QTc prolongation and required a European wide warning for quetiapine's use with other QTc prolonging drugs in January 2006.

799. In the United Kingdom, the quetiapine label contained warnings related to quetiapine's use with other QTc prolonging drugs since 1997.

800. The Court in *Wyeth* also squarely **rejected** Wyeth's suggestion that "the FDA, rather than the manufacturer bears primary responsibility for drug labeling," and provided a useful overview of the respective responsibilities of manufacturers and the FDA for what is contained in a drug's label.

801. First, the Court stated that "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. [The manufacturer] is charged with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* Importantly, the Court expressly emphasized that, "**prior to 2007, the FDA lacked the authority to order manufacturers to revise their labels.**" (emphasis added).

802. The Court further noted that when Congress granted the FDA this authority, "it **reaffirmed the manufacturer's obligations** and referred specifically to the CBE regulation, which both reflects **the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval.**" (emphasis added).

803. In June 2011, the FDA used this **authority to order AZ to include new, and stronger, warnings related to the use of quetiapine with other drugs known to cause increases in the QTc interval.**

804. From 1997 onwards, AZ should have included language in the United States quetiapine labels concerning quetiapine's known effect for increasing the QTc interval in order to protect Medicaid beneficiaries, Medicare Part D beneficiaries, all beneficiaries of federally funded insurance plans and the public at large from the known risk of ingesting quetiapine with drugs known to increase the QTc interval. Instead, AZ disseminated false and misleading information to Drug Utilization Review Boards and the public at large (including physicians and pharmacists) that quetiapine was safe to use concomitantly with other drugs known to increase the QTc interval.

805. Put simply, at no point has AZ **ever proposed any warning language** about the concomitant use of quetiapine with other drugs known to cause increases in the QTc interval with which the FDA disagreed or didn't result in a warning related to the concomitant usage of quetiapine with QT/QTc prolonging drugs.

806. Importantly, in *Wyeth*, neither Wyeth nor the United States was able to identify a case where the FDA brought an enforcement action against a manufacturer for **strengthening** a warning pursuant to the CBE regulation.

807. As the Court in *Wyeth* expressly observed, "the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept."

808. Here, AZ cannot credibly pretend that the FDA would not have approved the added warnings to the quetiapine labeling, especially given the clear evidence throughout the time period showing that the use of quetiapine with QT/QTc prolonging drugs was dangerous as well as the added warnings that had already **been included and required in other countries**.

809. Like the Phenergan label in the *Wyeth* case, the record lacks "any evidence that

the FDA set a ceiling” on quetiapine labeling relative to the dangers associated with quetiapine and QT/QTc interval prolongation or the dangers associated with taking quetiapine with drugs known to increase the QT/QTc interval. In fact, as discussed *supra*, the FDA rejected both AstraZeneca’s January 2010 CBE label language and its own reviewer’s label changes when it mandated that the “should be avoided” label language be included in both the Seroquel and Seroquel XR labels in June 2011.

810. There is no evidence that AZ attempted to make any change to its quetiapine labels to strengthen the warning concerning the concomitant use of quetiapine with other drugs known to increase the QTc interval prior to January 2010.

811. To the contrary, the evidence shows that AZ identified and feared what AZ considered potential “FDA label threats” regarding Seroquel and QTc prolongation as early as December 2000. Yet, AZ failed to amend the label to address these known risks for drug utilizations review boards, which place material reliance on the labeling to help ensure the safety of Medicaid beneficiaries.

812. Both the June 2003 and April 2010 Corporate Integrity Agreements AstraZeneca entered into with the United States government were aimed at ensuring that AstraZeneca comply with all statutes, regulations, and written directives of the Medicare, Medicaid, Federal health programs and FDA. The April 2010 Corporate Integrity Agreement reads in relevant part:

I. PREAMBLE

AstraZeneca Pharmaceuticals LP and AstraZeneca LP (collectively “AstraZeneca”) hereby enter into this Corporate Integrity Agreement (CIA) with the Office of Inspector General (OIG) of the United States Department of Health and Human Services (HHS) to promote compliance with the statutes, regulations, and written directives of Medicare, Medicaid, and all other Federal health care programs (as defined in 42 U.S.C. § 1320a-7b(f)) (Federal health care program requirements) and with the statutes, regulations, and written directives of the Food and Drug Administration (FDA requirements). Contemporaneously with this CIA, AstraZeneca is entering into a Settlement Agreement with the United States. AstraZeneca will also enter into settlement agreements with various States (State Settlement Agreement and Release) and AstraZeneca’s agreement to this CIA is a condition precedent to those agreements.

813. Furthermore, both the June 2003 and the April 2010 Corporate Integrity Agreements required that AstraZeneca certify that it is compliant with Federal health care program requirements, FDA requirements, and the obligations of the Corporate Integrity Agreements. The applicable section of the 2010 CIA reads in its entirety:

4. *Management Accountability and Certifications:* In addition to the responsibilities set forth in this CIA for all Covered Persons, certain AstraZeneca employees (“Certifying Employees”) are specifically expected to monitor and oversee activities within their areas of authority and shall annually certify, in writing or electronically, that the applicable AstraZeneca component is compliant with Federal health care program requirements, FDA requirements, and the obligations of this CIA. These Certifying Employees shall include, at a minimum, the following individuals from AstraZeneca: President, U.S. Business; vice presidents of commercial functions (including those vice presidents with sales, marketing and brand responsibilities); sales directors (including national sales directors, area sales directors, and regional sales directors); senior brand leaders (commercial brand leaders and development brand leaders); the Vice President of Medical Affairs and direct reports with responsibilities for Medical Affairs or Field Medical Relations; and the Executive Director of Promotional Regulatory Affairs.

814. By failing to amend the Seroquel and Seroquel XR labels to reflect the results of the Uehlinger study and quetiapine’s known effect on the QTc interval, AstraZeneca was in violation of the applicable statutes, regulations and written directives of the Medicare, Medicaid,

Federal health programs, and the Food and Drug Administration and the terms of both its June 2003 and April 2010 Corporate Integrity Agreements with the United States Government.

815. Accordingly, the concomitant use of quetiapine with methadone, and other drugs known to cause increases in the QTc interval, posed a grave and heretofore unknown health risk to patients, physicians and government payors. If physicians knew of this risk, they would not prescribed quetiapine (Seroquel or Seroquel XR) with drugs known to increase the QTc interval. If pharmacists knew of this risk, they would have taken steps to warn both the patient and the physician about this risk as well as refuse to fill the prescriptions. If state Medicaid Drug Utilization Review Boards had known of this risk, they would have directed that such use was **contraindicated** to prevent such usage (through, for example, the prior authorization process) and, in doing so, would have refused to pay the claim.

816. AstraZeneca had an obligation to disclose, and to accurately represent, to physicians, pharmacists, state Medicaid Drug Utilization Review boards and the public at large information related to the safety and risks of the concomitant use of quetiapine (Seroquel and Seroquel XR) and methadone.

817. AstraZeneca had an obligation to disclose and to accurately represent to physicians, pharmacists, state Medicaid Drug Utilization Review boards and the public at large information related to the safety and risks of quetiapine's effect on the QTc interval and the safety of using quetiapine concomitantly with drugs known to increase the QTc interval.

818. AstraZeneca's failure to disclose this risk and its misrepresentations of this risk misled physicians, pharmacists and state Medicaid Drug Utilization Review boards to believe that the concomitant use of quetiapine (Seroquel and Seroquel XR) with drugs known to prolong the QTc interval was devoid of any dangerous pharmacodynamic drug-drug interaction.

819. AstraZeneca's failure to warn of quetiapine's effect on the QTc interval misled physicians, pharmacists, Drug Utilization Review Boards, and patients to believe that the use of Seroquel with QT/QTc prolonging medications was safer than it truly was.

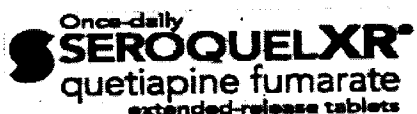
820. AstraZeneca's failure to warn of quetiapine's effect on the QTc interval caused Drug Utilization Review Boards to authorize payment for quetiapine prescriptions filled concomitantly with other drugs that increase the QTc interval.

821. Because of the danger associated with this usage, any time Seroquel or Seroquel XR has been prescribed concomitantly with methadone or any other drug known to cause an increase in the QTc interval, and such prescription was paid for by government funds, a false claim was submitted because, had the government payors, pharmacists or physicians known of this concealed and grave risk, approval would never have been granted for payment for the prescription.

L. At least ten deaths associated with the concomitant use of Seroquel and methadone at Staten Island, New York methadone clinics

822. Despite AstraZeneca knowing about the clear danger of using Seroquel or Seroquel XR with methadone (including an FDA Safety Alert for methadone), it nevertheless directs and incentivizes its representatives, including Plaintiff-Relator, to sell Seroquel and Seroquel XR to physicians, including primary care physicians, addiction specialists, pain specialists, physicians who practice at in-patient methadone clinics, and physicians who practice at out-patient methadone clinics, all of whom AstraZeneca knows prescribes Seroquel or Seroquel XR concomitantly with methadone.

823. On April 4, 2010, AstraZeneca distributed a document to the Seroquel XR sales force, which included Plaintiff-Relator, that specifically identified these physicians as targets for the promotion of Seroquel XR:



CNS Seroquel XR EarlyView Report

Seroquel XR Brand Market Definition & Alignment

Brand Market Definition: Abilify Oral, Geodon Oral, Saphris, Invega, Risperdal Oral, Risperidone, Seroquel IR, Seroquel XR, Symbyax & Zyprexa/ Zydol Oral.

CNS Alignment: CNS Seroquel XR EarlyView Report reflects the sales performance based on Zip to Terr.

15 Specialties in Psych Seroquel XR basket

15 Specialties Include: Addiction Medicine, Child & Adolescent Psych, Child Psych - Pediatrics, Family Practice - Psych Internal Medicine - Psych, Psych, Forensic Psych, Psychoanalysis, Geriatric Psych, Psych/ Neurology, Pain Medicine, Neurology, Internal Medicine - Neurology, Neuro Surgery & Neurology/ Psych Med and Rehab

Seroquel XR New Blocking rules: Customers Included

Psych Customers Zip To Terr.

Excludes Hospital Retail Physicians Block List and Physician Block Lists provided by Brand Team & Legal.

Includes PCPs, NPs & PAs on most recent lock down CSTP.

Note: Some Neuros and CHPs inclusion is incumbent upon patient population.

Report Owner:	Field Sales Analytics
Weekly Date:	03/19/10
Date Created:	04/06/10

15 Specialties in Psych Seroquel XR basket

15 Specialties Include: Addiction Medicine, Child & Adolescent Psych, Child Psych - Pediatrics, Family Practice - Psych Internal Medicine - Psych, Psych, Forensic Psych, Psychoanalysis, Geriatric Psych, Psych/ Neurology, Pain Medicine, Neurology, Internal Medicine - Neurology, Neuro Surgery & Neurology/ Psych Med and Rehab

824. Upon information and belief, AstraZeneca targeted these physicians since 1997.

825. At the direction of AstraZeneca, Plaintiff-Relator has provided Seroquel and Seroquel XR samples to four separate practices containing physicians that AstraZeneca knows prescribe Seroquel and/or Seroquel XR concomitantly with methadone:

- Staten Island University Hospital ("SIUH"), South Site, 392 Seaside Avenue, Staten Island, NY
- SIUH, North Site, 450 Seaside Avenue, Staten Island, NY
- Bridge Back to Life, 1688 Victory Boulevard, Staten Island, NY
- Richmond University Medical Center, MICA, 75 Vanderbilt Avenue, Staten Island, NY

826. AstraZeneca directs its representatives across the country to promote Seroquel and Seroquel XR to physicians AstraZeneca knows prescribe Seroquel or Seroquel XR concomitantly with methadone.

827. A physician at SIUH, Dr. Swarnamba Mani, told Ms. Zayas about one of those patients and offered that she believed Seroquel "played a role" in her patient's death.

828. Ms. Zayas reported this death to AstraZeneca's Product Manager for Safety Surveillance, Michele Gelman, in December 2009. The email correspondence between Ms. Zayas and Ms. Gelman reads as follows:

To: Gelman, Michele
Subject: RE: 2009SE22805/ SEROQUEL/ Dr. Mani Swarnamba/ Phone number requested
 Hi Michele,

I spoke to Dr. Mani back when the case was reported and she stated that she wanted no part in reporting anything for it wasn't her patient, but once she saw briefly. Because I had an obligation to report it, I did anyway and let her know that I had to since she did say she believed Seroquel may have played a role in this gentleman's death. Dr. Mani's phone number is [REDACTED]. She is part of an outpatient clinic and works standard hours. I doubt she'll respond or provide you the info you are looking for, as she wouldn't provide me with it, so don't be surprised. If there is anything else I can do to help, please feel free to contact me on my cell at [REDACTED]. I will try to make it a point to speak to the director of Staten Island University Hospital to see if I can get anymore information.

Thanks.
 Allison

-----Original Message-----
From: Gelman, Michele
Sent: Monday, December 28, 2009 11:46 AM
To: Zayas, Allison
Subject: 2009SE22805/ SEROQUEL/ Dr. Mani Swarnamba/ Phone number requested

Dear Allison,
 You were kind enough to report a case (Male pt. age and initials not provided) involving SEROQUEL to the PS department. I require some additional information from Dr. Swarnamba. Would you be able to give me a current phone number?
 I am looking for a cause of death, indication for use, dosage and dates of use for SEROQUEL, past medical history (drug abuse, cardiac dx) and autopsy results if one was done.

Happy holidays,
 Michele

Michele Gelman
 Product Manager, Safety Surveillance

Astrazeneca Pharmaceuticals
 Clinical Development, Patient Safety
 FOC, W2 583, Wilmington DE 19850, USA
 Tel +1-302-885-8381
 michele.gelman@astrazeneca.com

829. In early July 2010, Plaintiff-Relator was informed by Robert Schaer, the director of SIUH psychiatry clinics, that ten patients at SIUH clinics who were on methadone died unexpectedly within the previous year. The one common denominator for these deaths was that all the patients were on Seroquel.

830. On July 6, 2010, Ms. Zayas reported the following to AZ:

9. Please provide a Narrative Description of the Events:
 SEVERAL PHYSICIANS AT SIUH HAVE STATED SOMEONE DIED WHILE ON THE COMBINATION OF SEROQUEL AND METHADONE LATE LAST YEAR. AT THAT TIME, I SUBMITTED AN AE REPORT. SINCE THEN THE DIRECTOR HAS RESTATED THAT NUMBER SAYING SEVERAL MORE PEOPLE AND AS MANY AS 10 HAVE DIED WHILE ON THAT COMBINATION. A PIR WAS SUBMITTED LAST YEAR. I AM TOLD THE HOSPITAL HAD A MEETING REGARDING THESE INCIDENTS AND WILL NOT BE WRITING SEROQUEL OR SEROQUEL XR FOR ANY PATIENTS WHO ARE ON METHADONE.

Tracking:	Recipient	Read
	Patient Safety General Issues (Prof Serv, QA, etc)	Read: 7/7/2010 9:09 AM
	Wilmington	

831. Ms. Zayas's email is important for two distinct reasons. First, Ms. Zayas informs AZ that a "PIR," or product information request, was submitted by her in response to her first adverse event report reported by Dr. Swarnamba Mani in December 2009. Presumably, AZ sent a medical letter to Dr. Mani at that time about the concomitant use of quetiapine and methadone that mirrored the one sent to Dr. Doe. Secondly, it establishes definitively that as of July 7, 2010, at 9:09 a.m. AZ had knowledge of the ten deaths attributable to the concomitant use of quetiapine and methadone.

832. In fact, three physicians at SIUH now believe that quetiapine played a role in the deaths of the ten SIUH patients who took quetiapine and methadone concomitantly: Dr. Swarnamba Mani, Dr. Eileen Sweeney, and Dr. Robert Walter.

833. Prior to January 2010, there were no warnings whatsoever in the Seroquel labels to warn physicians, pharmacists, and the New York State Drug Utilization Review Board (or any other State Drug Utilization Review Board) of the dangers associated with the use of Seroquel with the QT/QTc prolonging drug methadone.

834. When a New York doctor specifically asked for information about the concomitant use of methadone and Seroquel, AstraZeneca withheld safety information from him related to Seroquel's effect on the QT/QTc interval when used with QT/QTc prolonging drugs.

835. Consequently, these patients had their quetiapine prescriptions filled with their

methadone prescriptions predicated on the false pretense that the concomitant use of the two medications was safe as it related to QT prolongation.

836. Upon information and belief, these patients were New York State Medicaid beneficiaries.

837. Dr. Walter's concerns prompted him to petition SIUH's Pharmacy and Therapeutic ("P&T") committee to remove Seroquel from the hospital's formulary.

838. Ms. Zayas's partner, Lori Gorman, circulated a petition at SIUH to keep Seroquel on the hospital's formulary. Although Ms. Zayas's partner has knowledge of the ten deaths associated with quetiapine and methadone, presumably she has no knowledge of the results of the Uehlinger study or the dangers associated with the concomitant usage of quetiapine with a known QT/QTc prolonging agent.

839. On June 24, 2010, or some twelve months before the Seroquel label was amended to include language advising that the use of Seroquel should be avoided with drugs known to cause increases in the QTc interval, SIUH's P&T committee published a document that was distributed throughout SIUH titled: "QT Drug Lists by Risk Groups -Drugs that Prolong the QT Interval and/or induce Torsades de Pointes Ventricular Arrhythmia" ("QT Warning Poster"). Ms. Zayas saw the document posted in Dr. Yelena Belyayeva's office.

840. The document contains a definition of torsades de pointes which reads: "Drug induced torsades de pointes (TdP), a specific type of ventricular arrhythmia that is associated with prolongation of the QTc interval, is a form of drug toxicity." Furthermore, the document advises the physicians to ask themselves three questions when prescribing one of the medications on the list:

- Has the patient had an EKG performed?
- Have you checked the EKG prior to administration?

- Is the patient already on one or more the medications listed below?

841. The QT Warning Poster lists methadone under the "Definite risk as a single agent" heading. Seroquel is listed under the "High Risk" heading.

842. The QT Warning Poster reads in relevant part:

QT Drug Lists by Risk Groups Drugs that Prolong the QT Interval and/or Induce Torsades de Pointes Ventricular Arrhythmia

Drug-induced torsades de pointes (TdP), a specific type of ventricular arrhythmia that is associated with prolongation of the QT interval, is a form of drug toxicity.

- Has the patient had an EKG performed?
- Have you checked the EKG prior to administration?
- Is the patient already on one or more of the medications listed below?

High Risk

Quetiapine

Seroquel®

Anti-psychotic / schizophrenia



Staten Island
University Hospital

Pharmacy & Therapeutic Committee

June 24, 2010

843. In contrast to SIUH, AZ represented in numerous representations to State Medicaid Plans that neither Seroquel nor Seroquel XR pose a "High Risk" for causing QTc prolongation in patients. The new label, mandated by the FDA, advises that use of Seroquel with a drug like methadone should be "avoided."

844. The QT Warning Poster was distributed as a direct result of the ten deaths of patients who died while taking methadone and Seroquel concomitantly.

845. Since at least June 2007, AstraZeneca has known that a quetiapine dose of 138 mg can cause up to an 85% increase in a patient's (R)-methadone levels.

846. AstraZeneca has also known that the vast majority of patients taking Seroquel or Seroquel XR, including those taking methadone, ingest more than 138 mg per day.

847. However, at no point in her tenure at AstraZeneca was Ms. Zayas been informed

of the potentially dangerous consequences of the concomitant use of methadone and Seroquel and Seroquel XR.

848. At no point in her tenure at AstraZeneca was Ms. Zayas informed about the dangers associated with the use of Seroquel with other drugs known to increase the QTc interval.

849. Furthermore, at no point has AstraZeneca ever informed physicians of the potential fatal consequences of the concomitant use of methadone and Seroquel and Seroquel XR. Instead, AstraZeneca made false statements in both the labels for Seroquel and Seroquel XR and in medical letters to physicians to hide the true risk of drug-drug interaction between quetiapine and other drugs known to increase the QTc interval.

850. Despite the fact these risks have not been disclosed to physicians who AZ knows prescribe methadone for both pain relief and for methadone maintenance treatment, AZ nevertheless directs sales representatives to call on primary care physicians, addiction specialists, pain specialists and general psychiatrists who AZ knows concomitantly prescribe methadone (and other drugs known to increase the QT/QTc interval) and quetiapine.

851. In fact, AstraZeneca sales representatives have called on and provide samples to pain specialists and addiction specialists.

852. In August 2010, Plaintiff-Relator met with her District Manager Donna Biller and her Regional Director James Ader at the LaGuardia Marriott in Elmhurst, NY (in Queens borough in New York City) and expressed concern about the deaths in Staten Island.

853. Despite Plaintiff-Relator's concerns about the ten deaths that occurred in Staten Island in patients taking Seroquel/Seroquel XR and methadone, James Ader nevertheless directed her to continue selling Seroquel and Seroquel XR to physicians that AstraZeneca knew used Seroquel and Seroquel with QT/QTc prolonging medications including, but not limited to,

methadone. These physicians included physicians that reported the deaths at Staten Island University Hospital.

854. Below is a sample of pain specialists and addiction specialists from New York, New Jersey, and Connecticut with their name, address, the number of sales representative calls made on them, the number of samples they received, and the “new” Seroquel XR prescriptions these physicians wrote from January 2008 through August 2009:

Name	Address	Sales rep calls	Samples	New SQL XR Scripts
Dr. Ulla Laasko – Addiction	910 Park Ave., New York, NY	129	1487	473
Dr. Jianping Chen - Addiction	268 Canal St., New York, NY	56	336	107
Dr. Emmanuel Hriso -Addiction	54 Main St., Woodbridge, NJ	26	548	33
Dr. Everett Hill –Addiction	2100 Westcott Drive, Flemington, NJ	36	433	14
Dr. Raul Calicdan - Addiction	506 Malcolm X Blvd, New York, NY	35	110	13
Dr. Peter Litwin –Addiction	628 Shrewsbury Ave., Ste J, Tinton Falls, NJ	26	159	12
Name	Address	Sales rep calls	Samples	New SQL XR Scripts
Dr. Imtiazuddin Siddiqui – Addiction	252 Washington Valley Rd., Randolph, NJ	30	133	11
Dr. John J. Wilkins - Addiction	1 Route 73 S, Marlton, NJ	30	435	9
Dr. Douglas Marcus- Addiction/Adolescent Psychiatry	151 Broadway, Amityville, NY	24	145	9
Dr. Clifford Jones –Addiction	34 E Main St., Marlton, NJ	24	184	5
Dr. John Cooke –Addiction	201 Lyons Ave., Newark, NJ	14	102	3
Dr. Zulfiqar Ali Rajput – Addiction/Geriatric	1541 Route 88 W, Ste J, Brick, NJ	30	150	2
Dr. Luz Green – Addiction/Neurology	352 77 th St., Brooklyn, NY	29	185	1
Dr. Richard Deworsop – Pediatric Psychiatry/Addiction	1163 Route 37 W, Ste C1, Toms River, NJ	36	488	107
Dr. Julio Del Castillo - Addiction	700 Airport Rd., Lakewood, NJ	33	135	51

Dr. Leonid A Izrayelit – Addiction	1725 E 12 th St, Ste 201, Brooklyn, NY	18	326	51
Dr. Vladimir Klebanov – Addiction	2044 Ocean Ave., Brooklyn, NY	21	386	37
Dr. Delfin Ibanez – Addiction	270 State Route 35, Red Bank, NJ	24	257	32
Dr. David Sikowitz – Addiction/Eating Disorders	661 Shrewsbury Ave., Shrewsbury, NJ	21	217	32
Dr. Camilo Serrano - Addiction	500 S. Pennsville Auburn Rd, Penns Grove, NJ	19	163	31
Dr. Vladimir Glauberson – Addiction	521 Beach 20 th St., Far Rockaway, NY	29	130	28
Dr. Lyubov Gorelik - Addiction	2601 Ocean Parkway, Brooklyn, NY	22	104	15
Dr. Arthur Africano – Addiction	147 East Ave., Norwalk, CT	14	207	15
Dr. Barry Glasser – Pain Management	4248 Harbour Beach Blvd., Brigantine, NJ	11	256	14
Dr. Prakash Amin – Addiction/Geriatric	221 Whitehorse-Mercerville Road Trenton, NJ	30	471	42
Dr. Jain Sanjeevani – Addiction/Pediatric	89 Sparta Avenue Sparta, NJ	33	112	40

855. Upon information and belief, each of these physicians prescribed Seroquel concomitantly with other drugs known to increase the QT/QTc interval, including methadone.

856. Thus, from January 2008 through August 2009, these physicians who specialized in either pain or addiction were collectively called on by AZ representatives **800 times**, received **4614 Seroquel XR samples** and wrote **1181** “New” off-label, and dangerous, prescriptions. These “New” prescriptions do not account for subsequent refills of these prescriptions.

857. At no point did AstraZeneca specifically warn any of these physicians of the inherent danger of using quetiapine with other drugs known to increase the QT/QTc interval, such as methadone.

858. In light of the wide utilization of methadone for both methadone maintenance

treatment and pain relief, these physicians unwittingly prescribed Seroquel or Seroquel XR to methadone patients, thus exposing the patient to a potential fatal overdose.

859. In light of the wide utilization of methadone for both methadone maintenance treatment and pain relief, these physicians unwittingly prescribed Seroquel or Seroquel XR to methadone patients, thus exposing the patient to a fatal cardiac arrhythmia.

860. In both the labeling for Seroquel and Seroquel XR and medical letters to physicians, AstraZeneca has deliberately concealed from physicians the dangers associated with the concomitant use of Seroquel or Seroquel XR and methadone. This purposeful concealment has led physicians to erroneously conclude that Seroquel and Seroquel XR were safe choices for patients taking methadone.

861. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QT/QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QT/QTc interval, thus exposing Medicaid beneficiaries to dangerous cardiac events.

862. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QT/QTc prolonging agents, physicians, and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QT/QTc interval. Furthermore, Drug Utilization Review Boards would have refused to authorize payment for them.

M. April 5, 2010 CNS XR EarlyView Report and Off-label promotion of Seroquel XR as monotherapy in major depression

863. AstraZeneca sales representatives, including Plaintiff-Relator, receive an "EarlyView" report that provides the sales data for Seroquel XR.

864. AstraZeneca records the sales data for the following medications: Abilify Oral,

Geodon Oral, Saphris, Invega, Risperdal Oral, Risperidone, Seroquel, Seroquel XR, Symbyax, and Zyprexa. This sales data is used in calculating sales representatives' bonuses.

865. AZ also monitors the prescribing history of fifteen different specialties in the "Psych Seroquel XR basket" for the purpose of tracking market share and ranking representatives for their sales and for bonus payouts.

866. Representatives are ranked according to their success in selling to each of different specialties and are incentivized to sell Seroquel and Seroquel XR with no consideration for whether the sale is for an on-label, off-label, or inherently dangerous purpose.

867. Because of Seroquel XR's limited indications, physicians in six of the identified specialties – Addiction Medicine, Child & Adolescent Psychiatry, Child Psychiatry, Pain Medicine, Neurology and Neurosurgery - can only prescribe the drug for off-label and/or inherently dangerous purposes that, in some cases, can lead to death.

868. Nevertheless, AstraZeneca directs and incentivizes its sales representatives to call on these physicians to promote Seroquel XR.

869. AstraZeneca also tracks the prescribing habits of geriatric psychiatrists and incentivizes representatives to sell Seroquel and Seroquel XR to those physicians.

870. Like all the other specialties in the "Seroquel XR basket," AstraZeneca directs and incentivizes its sales representatives to sell Seroquel and Seroquel XR to geriatric psychiatrists:

15 Specialties in Psych Seroquel XR basket

15 Specialties include: Addiction Medicine, Child & Adolescent Psych, Child Psych - Pediatrics, Family Practice - Psych Internal Medicine - Psych, Psych, Forensic Psych, Psychoanalysis, Geriatric Psych, Psych/ Neurology, Pain Medicine Neurology, Internal Medicine - Neurology, Neuro Surgery & Neurology/ Psych Med and Rehab

871. A geriatric psychiatrist is a medical doctor with special training in the diagnosis

and treatment of mental disorders that may occur in older adults. These disorders include, but are not limited to, dementia, depression, anxiety, and late-life schizophrenia.

872. Seroquel XR is indicated for adjunctive therapy for depression, bipolar disorder, and schizophrenia. It is not, however, indicated for the treatment of major depressive disorder as monotherapy, dementia, or anxiety.

873. Nevertheless, AstraZeneca directed its sales representatives to promote Seroquel XR for monotherapy depression.

874. For example, on August 19, 2009 at 8:21 p.m., Plaintiff-Relator's district manager at the time, Patrick O'Connell, directed Plaintiff-Relator and her partner Lori Gorman to promote Seroquel XR for monotherapy depression. The regional manager, James Ader, was copied on the email. The email reads in its entirety:

-----Original Message-----
From: O'Connell, Brendan,
Sent: Wednesday, August 19, 2009 8:21 PM,
To: Zayas, Allison; Gorman, Lori
Cc: Ader, James,
Subject: Action Plan Around Performance
Importance: High

Lori and Allison,

This morning we sat down and talked about the direction of your business over the last two earlyview reports. We talked about the fact that you have an opportunity to have a great year, but it is dependent on what you do right now with your business. You both did a great job of analyzing where some of your gaps lie. Together we developed an action plan to address these opportunities.

- When we reviewed your top 20 customers we found that 65% had a decline in their XR Nrx data when you compared the previous 5 weeks to the current 5 weeks. We talked about some individual physicians from this group that will be essential to your long term success. Dr. Enikeev, Thomas, Idowu and Chen. We also made plans to increase PREP activity at key accounts like Sunset Park. I am confident that you can change the direction quickly with a focus on these top customers. We'll work together to gain their commitment.
- We also spoke about your key trialists that have yet to use XR. In particular we identified Dr Katz and Dr Ziyalan as important to this goal.
- We talked about your competition at BMS and the fierceness with which they approach the business. We must match their intensity every day when it comes to selling competitively.
- We also spoke about your 7-10 customers that have yet to prescribe the medication. Lori made the terrific point that, collectively they could push your business over the top, so we must continue to take a balance approach to the business.
- Finally, we have to make the absolute most of every face to face interaction with

1

customers. Each call should continue to be judged on the following criteria: Did I sell competitively vs. Abilify? Did I persuade the physician of Seroquel XRs, efficacy as a monotherapy antidepressant with a unique MOA, did I present the patient type in a way that will help them remember and did I close for action. Each of these are essential on every single call!

Lori and Allison, you are in a terrific position to have a record year, I look forward to tracking the progress you make on our plans. In the meantime Please let me know if I missed anything.

Best Regards,

Brendan J. O'Connell
District Sales Manager
CNS Specialty Care-Brooklyn, NY
Cell: 860-539-6200
Audix: 70369

875. On August 31, 2009, James Ader responded to Mr. O'Connell's email to Plaintiff-

Relator and Lori Gorman. His email reads in its entirety:

From: Ader, James
Sent: Monday, August 31, 2009 2:34 PM
To: O'Connell, Brendan; Zayas, Allison; Gorman, Lori
Subject: RE: Action Plan Around Performance

You are all looking at the right things. I have no doubt that you will finish the year strong. This has been a terrific launch so far and you will make it even better!

Jim

876. Importantly, Mr. Ader made no mention of the fact that Seroquel XR's application for approval for monotherapy for major depression was specifically rejected by the FDA on April 8, 2009.

877. Instead, Mr. Ader stated that "[y]ou are all looking at the right things" in the promotion of Seroquel XR that specifically included the off-label promotion of Seroquel XR.

878. Like all antipsychotics, both Seroquel and Seroquel XR have black box warnings for use in geriatric patients with dementia-related psychosis which reads:

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- Antipsychotic drugs are associated with an increased risk of death. (5.1)
- Quetiapine is not approved for elderly patients with Dementia-Related Psychosis. (5.1)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. SEROQUEL XR is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL XR (quetiapine fumarate) is not approved for the treatment of patients with dementia-related psychosis [see **Boxed Warning**].

879. Geriatric psychiatrists may be aware of this warning and may take it into account when determining what drug, if any, to prescribe to a patient with dementia-related psychosis.

880. Regardless, AstraZeneca should not, under any circumstances, promote Seroquel XR's off-label use by providing samples to geriatric psychiatrists that encourages them to prescribe Seroquel XR for this, or any, dangerous off-label usage.

N. AstraZeneca directs sales representatives to promote Seroquel and Seroquel XR to physicians who exclusively treat developmentally disabled patients

881. There are approximately 4.5 million persons in the United States who are classified as developmentally disabled.

882. AstraZeneca has successfully sold Seroquel and Seroquel XR for off-label use to "control symptoms" in developmentally disabled patients since 1998.

883. AstraZeneca has known that it has directed its sales force to promote the use of Seroquel and Seroquel XR to control the symptoms of patients with developmental disabilities for over six years.

884. A person with a developmental disability is defined as follows:

A person with a developmental disability is incapacitated in at least 3 of the following activities (ADD):

- Taking care of themselves (dressing, bathing, eating, other daily tasks)
- Speaking and being clearly understood
- Learning
- Walking/moving around
- Making decisions
- Living on their own
- Earning/managing income

885. Some types of developmental disabilities include spina bifida, autism, cerebral

palsy, mental retardation, and Prader-Willi syndrome. AstraZeneca promoted both Seroquel and Seroquel XR to treat these diseases despite the fact that neither Seroquel nor Seroquel XR has indications to treat any of these conditions.

886. None of the Compendia support the use of Seroquel or Seroquel XR in the treatment of spina bifida, autism, cerebral palsy, mental retardation, or Prader-Willi syndrome.

887. Patients with developmental disabilities are particularly susceptible to the dangerous side effects posed by the use of quetiapine.

888. Nevertheless, AstraZeneca directs and incentivizes its representatives to promote Seroquel and Seroquel XR to physicians who exclusively treat patients who are developmentally disabled.

889. Physicians have informed Plaintiff-Relator that they exclusively prescribe atypical antipsychotics off-label to treat symptoms associated with developmental disabilities like irritability, anger, agitation, aggression, and obsessive behavior. Neither Seroquel nor Seroquel XR has an indication to treat any of these symptoms.

890. In fact, the July 28, 2010 Untitled Letter from the FDA identifies that AstraZeneca promoted Seroquel for the relief of the symptoms of “sadness” and “loss of interest” stating in relevant part:

Page 2 of the leave behind sheet presents the case study of “**Catherine F.**,” a patient who is “**still experiencing unresolved symptoms of MDD including sadness and loss of Interest**” (emphasis in original). This presentation misleadingly suggests that Seroquel XR alleviates the specific MDD symptoms of sadness and loss of interest, when this has not been demonstrated by substantial evidence or substantial clinical experience. According to the Clinical Studies – Major Depressive Disorder, Adjunctive Therapy to Antidepressants section of the PI, the efficacy of Seroquel XR was measured using a total score (i.e., “The primary endpoint in these trials was change from baseline to week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item clinician rated scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) with total scores ranging from 0 (no depressive features) to 60 (maximum score).”). Thus, while Seroquel XR has been shown to improve the total MADRS score, the clinical trials were not designed to assess the impact of Seroquel XR on each individual domain of the MADRS instrument. The inclusion of the accompanying footnote, “Sadness and loss of interest are select symptoms of MDD based on *DSM-IV-TR* criteria” does not mitigate the misleading nature of this presentation.

891. Through its sales and marketing efforts, AstraZeneca has targeted physicians who treat developmentally disabled patients with sales calls and samples in support of Seroquel and Seroquel XR. AstraZeneca has directed its sales representatives to sell Seroquel and Seroquel XR by stating that both drugs relieve “symptoms” associated with developmental disabilities.

892. Additionally, AstraZeneca has targeted physicians with erroneous promotional messages that Seroquel XR can alleviate specific symptoms associated with major depressive disorder even though these claims are not supported by substantial clinical evidence or experience.

893. Plaintiff-Relator was directed by AstraZeneca to sell both Seroquel and Seroquel XR to numerous doctors that exclusively treated patients who were developmentally disabled.

894. For example, she was directed to sell both Seroquel and Seroquel XR to the following physicians who practiced at the Maimonides Medical Center in Brooklyn, NY who exclusively treated patients who were developmentally disabled:

- Dr Basilio Cordoba
- Dr Porfirio Villarin
- Dr Jaweed Husain

- Dr Alexander Trakhtman

895. The scheme to sell Seroquel and Seroquel XR to physicians who exclusively treated developmentally disabled patients was a **nationwide scheme** that raised concerns among many sales representatives in the company.

896. For example, during a 2010 regional sales meeting in Boston an AstraZeneca sales representative asked in an open meeting of all the Seroquel/Seroquel XR representatives from the northeastern United States “what AstraZeneca was going to do to fix the target lists” that included “**doctors who treat nothing but retarded patients**” and did not treat patients with diseases for which Seroquel XR was labeled.

897. The senior AstraZeneca compliance manager that fielded this question responded that he “would get back” to the representatives about this issue.

898. To date, and despite the promise to “get back” to address the concern about off-label promotion, AstraZeneca continues to direct its Seroquel XR sales representatives to target physicians who exclusively treat patients who are developmentally disabled and promote the use of Seroquel XR to treat the symptoms associated with developmental disabilities.

O. AstraZeneca directs sales representatives to sample Seroquel and Seroquel XR to physicians who exclusively use Seroquel and Seroquel XR for off-label purposes and dangerous purposes

899. Pharmaceutical companies provide samples to physicians in order to encourage physicians to use their products.

900. On July 1, 2002, AstraZeneca internally published a document titled “Product Samples – Policy VI-7.”

901. The document outlined the purpose of providing samples to physicians who are called on by AstraZeneca sales representatives.

902. For example, for AstraZeneca, samples are “intended to provide an opportunity for the physician and patient to determine tolerability and effectiveness prior to filling an entire prescription.” The document reads in relevant part:



Product Samples

Issued by: **AZ Business Policy Group**

Date Issued: **03/31/2000**

Date Revised: **07/01/2002**

3. Policy

3.1. General Statement

AZ is dedicated to ensuring that the Company and its employees comply with all applicable legal requirements and prohibitions in the distribution of samples. For purposes of this policy, “samples” means a unit of prescription drug that is not intended to be sold and is intended to provide an opportunity for the physician and patient to determine tolerability and effectiveness prior to filling an entire prescription. Marketing and Sales Personnel involved in the distribution of samples must familiarize themselves with the provisions of this policy, the PDMA and all applicable laws and Company procedures and training materials relating to samples.

903. Furthermore, the policy outlines AstraZeneca’s “state of mind” when distributing samples to physicians. The document states in relevant part:

- 3.2.4. The distribution of product samples by AZ to HCPs is intended to help the HCP evaluate the product in actual practice, and to enable the HRx to offer a small supply of medication to a patient who is beginning to take the product for the first time. AZ samples should be distributed with these objectives in mind.**

904. AstraZeneca incentivized its representatives to sell Seroquel XR, and Seroquel to

physicians AstraZeneca knew would prescribe the drugs for off-label purposes and inherently dangerous concomitant use.

905. As proof of this incentive, AstraZeneca had a “Seroquel XR basket” of specialties that could only prescribe Seroquel XR for off-label and/or dangerous purposes including physicians who specialized in “Addiction Medicine,” “Child & Adolescent (psychiatrists),” “Geriatric (psychiatrists),” “Pain Medicine (physicians),” and “Internal Medicine (neurologists)”:



CNS Seroquel XR EarlyView Report

Seroquel XR Brand Market Definition & Alignment

Brand Market Definition: Abilify Oral, Geodon Oral, Saphris, Invega, Risperdal Oral, Risperidone, Seroquel IR, Seroquel XR, Symbyax & Zyprexa/ Zydys Oral.

CNS Alignment: CNS Seroquel XR EarlyView Report reflects the sales performance based on Zip to Terr.

15 Specialties in Psych Seroquel XR basket

15 Specialties Include: Addiction Medicine, Child & Adolescent Psych, Child Psych - Pediatrics, Family Practice - Psych Internal Medicine - Psych, Psych, Forensic Psych, Psychoanalysis, Geriatric Psych, Psych/ Neurology, Pain Medicine Neurology, Internal Medicine - Neurology, Neuro Surgery & Neurology/ Psych Med and Rehab

Seroquel XR New Blocking rules: Customers Included

Psych Customers Zip To Terr.

Excludes Hospital Retail Physicians Block List and Physician Block Lists provided by Brand Team & Legal.

Includes PCPs, NPs & PAs on most recent lock down CSTP.

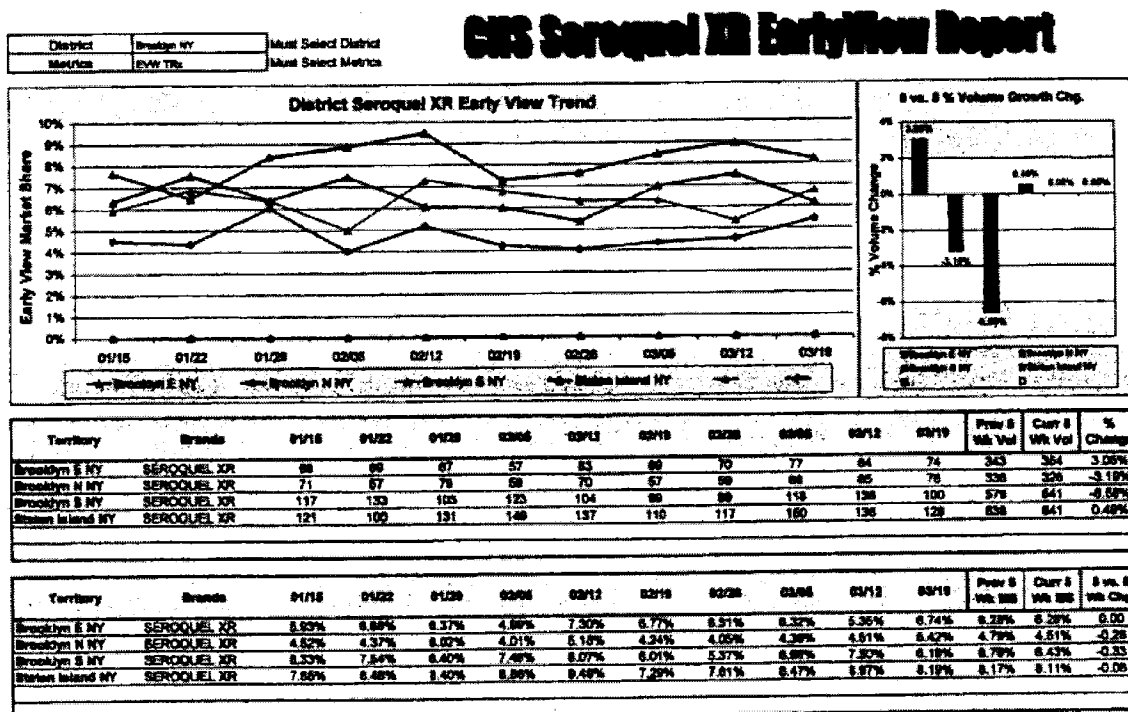
Note: Some Neuros and CHPs inclusion is incumbent upon patient population.

Report Owner:	Field Sales Analytics
Weekly Data:	03/19/10
Date Created:	04/05/10

15 Specialties in Psych Seroquel XR basket

15 Specialties Include: Addiction Medicine, Child & Adolescent Psych, Child Psych - Pediatrics, Family Practice - Psych, Internal Medicine - Psych, Psych, Forensic Psych, Psychoanalysis, Geriatric Psych, Psych/ Neurology, Pain Medicine, Neurology, Internal Medicine - Neurology, Neuro Surgery & Neurology/ Psych Med and Rehab

906. AstraZeneca tracked the sales of its representatives among physicians grouped in this “basket” of physicians with monthly tracking charts. The monthly tracking chart for Plaintiff-Relator’s territory, which included physicians who specialized in “Addiction Medicine”, “Child & Adolescent (psychiatrists)”, “Geriatric (psychiatrists)”, “Pain Medicine (physicians)”, and “Internal Medicine (neurologists)” was as follows:



907. Plaintiff-Relator would be penalized if she did not achieve target sales from physicians whose prescribing of Seroquel XR was off-label and/or inherently dangerous.

908. Dr. Stephen Kulick is a neurologist practicing at 1099 Targee Street, Staten Island, NY. Seroquel XR and Seroquel IR samples were distributed to Dr. Kulick on the following dates:

- Seroquel XR 50 mg February 9, 2009
- Seroquel IR 50 mg October 3, 2006
- Seroquel IR 100 mg October 3, 2006
- Seroquel IR 200 mg July 10, 2006

909. Dr. Aruna Agni is a child psychiatrist practicing at 657 Castleton Avenue, Staten Island, NY. Seroquel XR samples were distributed to Dr. Agni on the following dates:

- Seroquel XR 300 mg June 18, 2009
- Seroquel XR 150 mg June 18, 2009
- Seroquel XR 50 mg June 18, 2009
- Seroquel XR 200 mg June 18, 2009

- Seroquel XR 400 mg June 18, 2009
- Seroquel XR 50 mg April 16, 2009
- Seroquel XR 150 mg February 18, 2009
- Seroquel XR 50 mg February 18, 2009
- Seroquel XR 200 mg February 17, 2009
- Seroquel XR 400 mg February 17, 2009
- Seroquel XR 300 mg February 17, 2009

910. Dr. Allan Perel is a neurologist practicing at 27 New Drop Lane, Brooklyn, NY.

Seroquel XR samples were distributed to Dr. Perel on the following dates:

- Seroquel XR 50 mg October 9, 2009
- Seroquel XR 50 mg August 14, 2009
- Seroquel XR 50 mg April 9, 2009
- Seroquel XR 150 mg April 9, 2009
- Seroquel XR 150 mg March 19, 2009
- Seroquel XR 50 mg March 13, 2009

911. Dr. Anne Thomas is a child psychiatrist who practiced at 514 49th Street,

Brooklyn, NY and 2355 Ocean Avenue Brooklyn, NY. Seroquel XR and Seroquel samples were distributed to Dr. Thomas on the following dates:

- Seroquel XR 300 mg August 31, 2009
- Seroquel XR 150 mg August 31, 2009
- Seroquel XR 200 mg August 31, 2009
- Seroquel XR 400 mg August 31, 2009
- Seroquel XR 150 mg April 8, 2009
- Seroquel XR 50 mg April 8, 2009
- Seroquel XR 300 mg April 7, 2009
- Seroquel XR 150 mg April 7, 2009
- Seroquel XR 50 mg April 7, 2009
- Seroquel XR 200 mg April 7, 2009
- Seroquel XR 400 mg April 7, 2009
- Seroquel 300 mg January 28, 2009
- Seroquel 50 mg January 28, 2009
- Seroquel Starter Pak October 17, 2006
- Seroquel 100 mg October 17, 2006
- Seroquel 300 mg October 17, 2006
- Seroquel 200 mg October 17, 2006
- Seroquel 50 mg October 17, 2006
- Seroquel Starter Pak September 22, 2006

- Seroquel 100 mg September 22, 2006
- Seroquel 300 mg September 22, 2006
- Seroquel 50 mg September 22, 2006
- Seroquel Starter Pak July 17, 2006
- Seroquel 100 mg July 17, 2006
- Seroquel 300 mg July 17, 2006
- Seroquel 200 mg July 17, 2006
- Seroquel 50 mg July 17, 2006
- Seroquel 25 mg July 17, 2006
- Seroquel 100 mg July 12, 2006
- Seroquel 300 mg July 3, 2006
- Seroquel 200 mg July 3, 2006
- Seroquel 50 mg July 3, 2006
- Seroquel 25 mg July 3, 2006

912. Physicians gave these samples to patients along with a prescription.

Because of the physicians' specialty (*i.e.* child psychiatry, neurology), these prescriptions were for off-label purposes and claims were submitted to Medicaid for reimbursement.

913. By providing these samples to child psychiatrists and neurologists, AstraZeneca caused physicians to prescribe Seroquel and Seroquel XR for off-label uses.

P. The Federal False Claims Act

914. The Federal False Claims Act, 31 U.S.C. §§ 3729-32, prohibits the making of false or fraudulent claims for payment or approval, or causing such false or fraudulent claims to be made to the United States in connection with any program, such as Medicaid, which is funded, in whole or in part, by the United States.

915. In making, and causing to be made, claims for reimbursement under the Medicare and Medicaid programs for Seroquel and Seroquel XR, AstraZeneca caused to be submitted false and fraudulent claims in violation of the Federal, State, and City False Claims Acts by promoting Seroquel and Seroquel XR for off-label and dangerous purposes in the following ways:

- By failing to disclose the dangers associated with the use of Seroquel and Seroquel XR in the drugs' labels in patients taking methadone and other drugs known to increase the QT/QTc interval thus causing physicians to prescribe, pharmacists to fill and Medicaid to

authorize payment for quetiapine prescriptions prescribed concomitantly with drugs known to increase the QT/QTc interval;

- By disseminating false and misleading information to State Drug Utilization Review Boards concerning the safety of the concomitant use of quetiapine with other drugs known to increase the QT/QTc interval;
- By incentivizing representatives to promote and sample Seroquel and Seroquel XR to physicians, including, but not limited to, primary care physicians, pain physicians, and addiction specialists, who AstraZeneca knew prescribed Seroquel or Seroquel XR with methadone and QT/QTc prolonging medications without adequate warnings;
- By incentivizing representatives to promote and sample Seroquel and Seroquel XR to physicians AstraZeneca knew could only prescribe Seroquel and Seroquel XR for off-label purposes, including neurologists, child psychiatrists, addiction specialists, pain specialists, neurosurgeons, geriatric psychiatrists, and physicians who treat patients who are developmentally disabled.
- By promoting Seroquel and Seroquel XR for “symptom control” to physicians who treat patients who are developmentally disabled.
- By promoting Seroquel XR as monotherapy for major depression.
- By concealing evidence of quetiapine’s (inclusive of both Seroquel and Seroquel XR) effect on the QT/QTc from FDA, AstraZeneca ensured that the quetiapine labels would have no warnings proscribing the concomitant use of quetiapine with QT/QTc prolonging drugs thus increasing the sales of the drugs for dangerous uses.
- AstraZeneca concealed evidence of its own labeling decisions related to warnings on its Seroquel and Seroquel XR labels from two separate FDA Advisory Committees that AstraZeneca knew were concerned with quetiapine’s effect on the QT/QTc interval in an attempt to garner additional indications for Seroquel and Seroquel XR without adequate warnings.
- AstraZeneca concealed evidence from the FDA during its labeling negotiations with the FDA related to the January 2010 Changes Being Effected label change for QT/QTc prolongation in an attempt to prevent a “should be avoided” warning being placed on the Seroquel and Seroquel XR labels that would affect sales by causing Seroquel/Seroquel XR prescriptions with other QT/QTc prolonging medications to be rejected.

916. AstraZeneca’s willful and dangerous concealment of quetiapine’s deadly effect of prolonging the QT/QTc interval that can precipitate a fatal cardiac arrhythmia caused physicians to prescribe Seroquel concomitantly with drugs associated with prolonging the QT/QTc interval,

pharmacists to fill Seroquel prescriptions with drugs associated with prolonging the QT/QTc interval and Drug Utilization Review Boards to authorize payment for Seroquel prescriptions filled with drugs associated with prolonging the QT/QTc interval.

917. AstraZeneca also withheld the fact that it had strengthened the warnings for Seroquel and Seroquel XR related to QT/QTc prolongation from two separate FDA Advisory Committees.

918. If the label had been amended when there was “reasonable evidence of an association” between Seroquel and Seroquel XR and QT/QTc prolongation to include the warning the quetiapine label now has concerning its use with QT/QTc prolonging agents, physicians, pharmacists and state Medicaid Drug Utilization Review Boards alike would have refused to prescribe, fill and authorize payment for quetiapine with drugs associated with prolonging the QT/QTc interval. Accordingly, each time a physician wrote prescriptions resulting in the concomitant use of quetiapine and a drug known to increase the QT/QTc interval two separate false claims were submitted to the States – one for the QT/QTc prolonging drug and one for the quetiapine prescription.

919. If AstraZeneca, as opposed to the FDA, had amended the label earlier to include the warning the quetiapine label now has concerning its use with QT/QTc prolonging agents, the federal government would have refused authorization for payment for the quetiapine prescriptions that were filled concomitantly with other drugs known to increase the QT/QTc interval. Accordingly, each time a physician wrote prescriptions resulting in the concomitant use of quetiapine and a drug known to increase the QT/QTc interval two separate false claims were submitted to the federal government – one for the QT/QTc prolonging drug and one for the quetiapine prescription.

920. For each of these false claims, the United States government is entitled to recover a civil penalty of not less than \$5,000 and at least \$11,000, plus 3 times the amount of damages which the United States Government sustains for each prescription of methadone and each prescription of quetiapine that were concomitantly prescribed.

921. Upon information and belief, Defendant's illegal marketing practices in violation of the False Claims Act are being committed on a nationwide basis. Their illegal marketing practices resulted in the submission of false claims to Medicaid, CHAMPUS/TRICARE, CHAMPVA, the Federal Health Benefit Program, and other federal health care programs, including but not limited to, those administered by the State Plaintiffs in this case.

922. Upon information and belief, the Defendant's intentional violations of the False Claims Act related to Seroquel and Seroquel XR are ongoing, in spite of the recent investigation and settlement.

923. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

924. By virtue of the above-described acts, among others, Defendant has knowingly made or caused to be made false claims for Seroquel to the United States government.

925. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the federal government to approve and pay such false and fraudulent claims.

926. The federal government, unaware of the falsity of the records, statements and

claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid for but for Defendant's illegal inducements and/or business practices.

IV. CLAIMS FOR RELIEF

COUNT I **Violations of False Claims Act** **31 U.S.C. § 3729**

927. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

928. This Count is brought by Plaintiff-Relator in the name of the United States against the Defendant under the *qui tam* provisions of 31 U.S.C. § 3730 for Defendant's violation of 31 U.S.C. § 3729(a)(1) and (a)(2). In violation of 31 U.S.C. § 3729(a)(1) and (a)(2), Defendant made and caused to be made, the false claims that have been set forth in the Complaint herein.

929. Plaintiff United States, unaware of the falsity of the claims and/or statements which Defendant caused doctors, pharmacists, and other health care providers to make to the United States, and in reliance on the accuracy thereof, paid those doctors, pharmacies and other health care providers for claims that would otherwise not have been allowed.

930. The amounts of the false or fraudulent claims to the United States were material.

931. Plaintiff United States, being unaware of the falsity of the claims and/or statements made by Defendant, and in reliance on the accuracy thereof, paid and may continue to pay Defendant for health care services that otherwise should not have been paid under the Medicaid, CHAMPUS/TRICARE, CHAMPVA, and the Federal Health Benefit Program, and other federal health care programs.

932. The United States and the state Medicaid programs have been damaged by the payment of false or fraudulent claims.

933. By virtue of the above-described acts, among others, Defendant AstraZeneca did

knowingly and willfully fail to change the Seroquel and Seroquel XR labels to include warnings about the dangers posed when the drugs are used in combination with other QTc prolonging agents thus causing false claims to be submitted to the United States.

934. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the False Claims Act this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to three (3) times the amount of damages that the United States has sustained because of AstraZeneca's actions, plus a civil penalty not less than \$5,000 nor more than \$10,000 for each violation of 31 U.S.C. § 3729;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant to § 3730(d) of the False Claims Act and/or any other applicable provision of the law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT II

Defendant AstraZeneca's Violations Of The June 2003 and April 2010 Corporate Integrity Agreements With The United States

935. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

936. AstraZeneca has entered into two separate Corporate Integrity Agreements

(“CIAs”) with the United States Government wherein AstraZeneca was required to comply with all applicable FDA requirements concerning methods for selling, marketing, promoting, advertising, and disseminating information about off-label uses of AstraZeneca’s products.

937. As a result of its first CIA, AstraZeneca had to develop and implement a “Code of Conduct” that it had to follow. The Code of Conduct from April 2008 read in relevant part:

AstraZeneca’s policy is to disclose information in a timely manner, as necessary, to comply with all relevant legal and regulatory requirements. All such disclosures must be accurate and not misleading, with no material* omissions. This policy applies to all information, whether favourable or unfavourable to AstraZeneca.

938. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

939. By virtue of the above-described acts described herein, among others, Defendant AstraZeneca knowingly and willfully concealed “unfavourable” safety information concerning Seroquel and Seroquel XR from the FDA and provided misleading information to it concerning the safety of Seroquel and Seroquel XR.

940. AstraZeneca’s sales, marketing, promotional, regulatory and advertising efforts behind Seroquel and Seroquel XR were in violation of AstraZeneca’s June 2003 CIA with the United States government.

941. AstraZeneca’s sales, marketing, promotional, regulatory and advertising efforts

behind Seroquel and Seroquel XR have been and continue to be in violation of the April 2010 CIA.

942. AstraZeneca is now liable to the United States for penalties pursuant to the CIAs.

943. Because of Defendant's wanton disregard of the CIAs, it is now subject to debarment.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Corporate Integrity Agreements that this Court enter judgment, including all damages from said violations, and fines and penalties provided for under the Corporate Integrity Agreements, in Plaintiff's favor and against AstraZeneca for violation of the terms of said Agreements;

b. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

c. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT III
California False Claims Act
Cal. Government Code §§ 12650-12655

944. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

945. This is a claim against AstraZeneca for treble damages and penalties on behalf of the State of California under the California False Claims Act, California Government Code §§ 12650-12655.

946. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

947. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of California in extreme jeopardy. Had the State of California known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of California – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

948. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QT/QTc interval two separate false claims were submitted to the State of California – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

949. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused

payment for such concomitant usage unless a physician filed a prior authorization request that specifically asked for the use of two contraindicated drugs unless a physician filed a prior authorization request that specifically asked for the use of two contraindicated drugs. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

950. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

951. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

952. By virtue of the above-described unlawful acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the California State Government to approve and pay such false and fraudulent claims under the Medicaid program.

953. The California State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

954. By reason of Defendant's conspiracy and unlawful acts, the State of California has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

955. The State of California is entitled to the maximum penalty of \$10,000 for each

and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the California False Claims Act that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that California has sustained because of AstraZeneca's actions, plus a civil penalty of not more than \$10,000 for each violation of CAL. GOV. CODE §12651(a)(3);

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant to CAL. GOV. CODE §12652(g)(2) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT IV
Delaware False Claims and Reporting Act
6 Del C. §1201(a)(1) and (2)

956. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

957. This is a claim for treble damages and penalties against AstraZeneca on behalf of the State of Delaware under the Delaware False Claims and Reporting Act, 6 Del C. §1201(a)(1) and (2).

958. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

959. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine placed and continues to place residents and citizens of the State of Delaware in extreme jeopardy. Had the State of Delaware known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Delaware – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

960. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Delaware – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

961. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused

payment for such concomitant usage unless a physician filed a prior authorization request that specifically asked for the use of two contraindicated drugs unless a physician filed a prior authorization request that specifically asked for the use of two contraindicated drugs. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

962. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

963. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

964. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Delaware State Government to approve and pay such false and fraudulent claims.

965. The Delaware State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

966. By reason of Defendant's conspiracy and unlawful acts, the State of Delaware has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

967. The State of Delaware is entitled to the maximum penalty of \$11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

- a. That by reason of the aforementioned violations of the Delaware false claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that Delaware has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,500 and not more than \$11,000 for each violation of DEL. CODE ANN. TIT. 6 §1201(a)(3);
- b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant to DEL. CODE ANN. §1205(a) and/or any other applicable provision of law;
- c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and
- d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT V

**District of Columbia Procurement Reform Amendment Act
Violation of D.C. CODE ANN. §§ 2-308.13-.15**

968. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

969. This is a claim for treble damages and penalties against AstraZeneca on behalf of the District of Columbia under the District of Columbia Procurement Reform Amendment Act.

970. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

971. AstraZeneca's willful and reckless concealment of the dangerous consequences of

using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the District of Columbia in extreme jeopardy. Had the District of Columbia known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the District of Columbia – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

972. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the District of Columbia – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

973. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the District of Columbia's Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage unless a physician filed a prior

authorization request that specifically asked for the use of two contraindicated drugs. Instead, the District of Columbia's Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

974. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

975. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

976. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the District of Columbia Government to approve and pay such false and fraudulent claims.

977. The District of Columbia Government, unaware of the falsity of the records, statements, and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

978. By reason of the Defendant's unlawful acts, the District of Columbia has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

979. The District of Columbia is entitled to the maximum penalty of \$11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the District of Columbia false claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the District of Columbia has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of DC. CODE ANN. §2-308.14(a)(3);

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant DC. CODE ANN. §2-308.15(f)(1) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT VI
Florida False Claims Act
Fl. Stat. §68.081-68.090

980. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

981. This is a claim for treble damages and penalties against the Defendant on behalf of the State of Florida under the Florida False Claims Act, Fl.Stat. §68.081-68.090.

982. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

983. AstraZeneca's willful and reckless concealment of the dangerous consequences of

using methadone concomitantly with quetiapine placed and continues to place residents and citizens of the State of Florida in extreme jeopardy. Had the State of Florida known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Florida – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

984. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval, two separate false claims were submitted to the State of Florida – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

985. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State

Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

986. From 2008 to 2009, Florida Medicaid reported that 95,987 drug-drug alerts were recorded for quetiapine prescriptions filled concomitantly with drugs known to increase the QTc interval constituting more than 35% of all quetiapine prescriptions filled during this period.

987. From 2008 to 2009, the State of Florida spent approximately \$30,542,857.47 for quetiapine prescriptions filled concomitantly with other drugs known to cause QTc prolongation.

988. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

989. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

990. By virtue of the above-described acts, Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Florida State Government to approve and pay such false and fraudulent claims.

991. The Florida State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

992. By reason of the Defendant's unlawful acts, the State of Florida has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

993. The State of Florida is entitled to the maximum penalty of \$11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

- a. That by reason of the aforementioned violations of the Florida false claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that Florida has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of FLA. STAT. ANN. §68.082(2)(a)(3);
- b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant FLA. STAT. ANN. §68.085(1)-(2) and/or any other applicable provision of law;
- c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and
- d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT VII
Hawaii False Claims Act
HAW. REV. STAT. §§661-21 to 661-29

994. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

995. This is a claim for treble damages and penalties against the Defendant on behalf of the State of Hawaii under the HAW. REV. STAT. §661-21(a)(3).

996. By virtue of the above-described acts, among others, Defendant AstraZeneca

knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

997. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Hawaii in extreme jeopardy. Had the State of Hawaii known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Hawaii – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

998. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QT/QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QT/QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Hawaii– one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

999. Furthermore, if the label accurately reflected that the concomitant usage of

quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1000. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1001. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1002. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Hawaii State Government to approve and pay such false and fraudulent claims. The Hawaii State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1003. By reason of the Defendant's unlawful acts, the State of Hawaii has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1004. The State of Hawaii's Medicaid Program has been damaged by the payment of false and fraudulent claims.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Hawaii's false claim provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that Hawaii has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of HAW. REV. STAT. §661-21(a)(3);

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant HAW. REV. STAT. §661-27(a) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT VIII
Illinois Whistleblower Reward and Protection Act
740 ILCS 175/1 *et seq*

1005. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1006. This is a claim for treble damages and penalties against the Defendant on behalf of the State of Illinois under the Illinois Whistleblower Reward and Protection Act, 740 ILCS 17511 *et seq*.

1007. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1008. AstraZeneca's willful and reckless concealment of the dangerous consequences of

using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Illinois in extreme jeopardy. Had the State of Illinois known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Illinois – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1009. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Illinois – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1010. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State

Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1011. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1012. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1013. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Illinois State Government to approve and pay such false and fraudulent claims.

1014. The Illinois State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1015. By reason of the Defendant's unlawful acts, the State of Illinois has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1016. The State of Illinois is entitled to the maximum penalty of \$10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Illinois Whistleblower Reward and Protection Act that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that Illinois has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of ILL. COMP. STAT. 175/3(a)(3);

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant ILL. COMP. STAT. 175/4(d)(1) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT IX
Nevada False Claims Act
NEV. REV. STAT. ANN. §357.01-.250

1017. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1018. This is a claim for treble damages and penalties against the Defendant on behalf of the State of Nevada under the Nevada False Claims Act.

1019. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1020. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Nevada in extreme jeopardy. Had the State of Nevada known of the

extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Nevada – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1021. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Nevada – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1022. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false

information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1023. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1024. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1025. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Nevada State Government to approve and pay such false and fraudulent claims.

1026. The Nevada State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1027. By reason of the Defendant's unlawful acts, the State of Nevada has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1028. The State of Nevada is entitled to the maximum penalty of \$10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Nevada false claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in

an amount equal to not less than two times and not more than three times the amount of damages that Nevada has sustained because of AstraZeneca's actions, plus a civil penalty of not more than \$10,000 for each violation of the NEV. REV. STAT. ANN. §357.014(1)(c);

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant Nev. Rev. Stat. Ann. §357,210(1) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT X

**Tennessee Medicaid False Claims Act
Tenn. Code. Ann. §71-5-181 to -185**

1029. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1030. This is a claim for treble damages and penalties against the Defendant on behalf of the State of Tennessee under the Tennessee Medicaid False Claims Act.

1031. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1032. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Tennessee in extreme jeopardy. Had the State of Tennessee known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims

were submitted to the State of Tennessee – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1033. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Tennessee – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1034. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1035. By virtue of the above-described acts, among others, Defendant AstraZeneca

knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1036. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1037. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Tennessee State Government to approve and pay such false and fraudulent claims.

1038. The Tennessee State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1039. By reason of the Defendant's unlawful acts, the State of Tennessee has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1040. The State of Tennessee is entitled to the maximum penalty of \$10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Tennessee false claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that Tennessee has sustained because of AstraZeneca's actions, plus a civil penalty of not less

than \$5,000 and not more than \$10,000 for each violation of the TENN. CODE ANN. §71-5-182(a)(1)(C);

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant Tenn. Code. Ann. §71-5-183(c)(1) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XI
Virginia Fraud Against Taxpayer's Act
VA CODE ANN. 8.01-2.16. 1-216.19

1041. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1042. This is a claim for treble damages and penalties against the Defendant on behalf of the Commonwealth of Virginia under the Virginia Fraud Against Taxpayers Act, Vested. Ch. 842, Article 19.1, § 8.01-216.1 *et seq.*

1043. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1044. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the Commonwealth of Virginia in extreme jeopardy. Had the Commonwealth of Virginia known of the extreme danger presented by the concomitant use of methadone and

quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the Commonwealth of Virginia – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1045. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the Commonwealth of Virginia – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1046. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the Commonwealth Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the Commonwealth Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1047. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1048. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1049. By virtue of the above-described acts, Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Virginia State Government to approve and pay such false and fraudulent claims.

1050. The Virginia State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1051. By reason of the Defendant's unlawful acts, the State of Virginia has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1052. The State of Virginia is entitled to the maximum penalty of \$10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Virginia Fraud Against Taxpayers Act that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the Commonwealth of Virginia has sustained because of AstraZeneca's

actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of the VA. CODE ANN. § 8.01-216.3(A)(3);

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant VA. CODE ANN. § 8.01-216.7 and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XII
Georgia State False Medicaid Claims Act
Ga. Code 49-4-168 *et seq.*

1053. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1054. This is a claim for treble damages and penalties against the Defendant on behalf of the State of Georgia under the Georgia State False Medicaid Claims Act, Ga. Code 49-4-168 *et seq.*

1055. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1056. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Georgia in extreme jeopardy. Had the State of Georgia known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims

were submitted to the State of Georgia – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1057. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Georgia – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1058. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1059. By virtue of the above-described acts, among others, Defendant AstraZeneca

knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1060. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1061. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Georgia State Government to approve and pay such false and fraudulent claims.

1062. The Georgia State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1063. By reason of the Defendant's unlawful acts, the State of Georgia has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1064. The State of Georgia is entitled to the maximum penalty of \$11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Georgia False Medicaid Claims Act that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the Georgia has sustained because of AstraZeneca's actions, plus a civil penalty of not more than \$10,000 for each violation of the GA. CODE ANN. § 49-4-168.1;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant the GA. CODE ANN. § 49-4-168.2 (I) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XIII

Indiana State False Claims and Whistleblowers Protection Act, IND. CODE ANN. § 5-11-5.5-1 – 5-11-5.5-18

1065. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1066. This is a claim for treble damages and penalties against the Defendant on behalf of the State of Indiana under the Indiana State False Claims and Whistleblowers Protection Act, IND. CODE ANN. § 5-11-5.5-1 – 5-11-5.5-18.

1067. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1068. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Indiana in extreme jeopardy. Had the State of Indiana known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims

were submitted to the State of Indiana – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1069. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Indiana – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1070. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1071. By virtue of the above-described acts, among others, Defendant AstraZeneca

knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1072. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1073. By virtue of the above-described acts, Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Indiana State Government to approve and pay such false and fraudulent claims.

1074. The Indiana State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1075. By reason of the Defendant's unlawful acts, the State of Indiana has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Indiana State False Claims and Whistleblowers Protection Act that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the Indiana has sustained because of AstraZeneca's actions, plus a civil penalty of less than \$5,000 for each violation of the IND. CODE ANN. § 5-11-5.5-2;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant the IND. CODE ANN. § 5-11-5.5-6 and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XIV
Michigan Medicaid False Claims Act
MICH. COMP LAWS § 400.601-400.613

1076. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1077. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1078. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Michigan in extreme jeopardy. Had the State of Michigan known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Michigan – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1079. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc

interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Michigan – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1080. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1081. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1082. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1083. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Michigan State Government to approve and pay such false and fraudulent claims.

1084. The Michigan State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1085. By reason of the Defendant's unlawful acts, the State of Michigan has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1086. The Michigan State Medicaid Program has been damaged by the payment of false and fraudulent claims.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Michigan State Medicaid False Claims Act that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to three times the amount of damages that the Michigan has sustained because of AstraZeneca's actions, plus a civil penalty of equal to the full amount AstraZeneca unjustly received as a result of its unlawful conduct for violating MICH. COMP LAWS § 400.603, 606 and 607;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant the MICH. COMP LAWS § 400.610 and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XV
Montana False Claims Act
MONT. CODE ANN. § 17-8-401 – 17-8-412

1087. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1088. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1089. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Montana in extreme jeopardy. Had the State of Montana known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Montana – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1090. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of

quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Montana – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1091. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1092. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1093. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1094. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Montana State Government to approve and pay such false and fraudulent claims.

1095. The Montana State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1096. By reason of the Defendant's unlawful acts, the State of Montana has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1097. The Montana State Medicaid Program has been damaged by the payment of false and fraudulent claims.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Montana False Claims Act that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the Montana has sustained because of AstraZeneca's actions, plus a civil penalty of not more than \$10,000 for each violation of the MONT. CODE ANN. § 17-8-403;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant the MONT. CODE ANN. § 17-8-410 and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XVI
New Hampshire False Claims Act
N.H. REV. STAT. ANN. § 167:58-167:61-b

1098. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1099. This is a claim for treble damages and penalties against Defendants on behalf of the State of New Hampshire under the New Hampshire False Claims Act, N.H. REV. STAT. ANN. §167:61-b.

1100. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1101. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of New Hampshire in extreme jeopardy. Had the State of New Hampshire known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of New Hampshire – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1102. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of New Hampshire – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1103. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1104. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1105. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1106. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the New Hampshire State Government to approve and pay such false and fraudulent claims.

1107. The New Hampshire State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1108. By reason of the Defendant's unlawful acts, the State of New Hampshire has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1109. The State of New Hampshire is entitled to the maximum penalty of \$11,000 for

each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the New Hampshire false claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that New Hampshire has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of the N.H. REV. STAT. ANN. §167:61-b;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant N.H. REV. STAT. ANN. §167:61-b and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XVII
New Mexico Medicaid False Claims Act,
N.M. STAT. ANN. § 27-14-1- - 27-14-15

1110. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1111. This is a claim for treble damages and penalties against all Defendant on behalf of the State of New Mexico under the New Mexico Medicaid False Claims Act, N.M. STAT. ANN. § 27-14-1- 27-14-15.

1112. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1113. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of New Mexico in extreme jeopardy. Had the State of New Mexico known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of New Mexico – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1114. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of New Mexico – one for the drug known to cause increases in the QT/QTc interval and one for the quetiapine prescription.

1115. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1116. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1117. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1118. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the New Mexico State Government to approve and pay such false and fraudulent claims.

1119. The New Mexico State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1120. By reason of the Defendant's unlawful acts, the State of New Mexico has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

- a. That by reason of the aforementioned violations of the New Mexico False Claims Act provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount three times the amount of damages that New Mexico has sustained because of AstraZeneca's actions for violation of the N.M. STAT. ANN. § 27-14-4;
- b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant N.M. STAT. ANN. § 27-14-9 and/or any other applicable provision of law;
- c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and
- d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XVIII
New York False Claims Act
N.Y. St. Finance Law §187 *et seq.*

1121. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1122. This is a claim for treble damages and penalties against all Defendant on behalf of the State of New York under the New York False Claims Act, N.Y. St. Finance Law §187 *et seq.*

1123. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1124. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of New York in extreme jeopardy. Had the State of New York known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote

prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of New York – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1125. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of New York – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1126. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1127. By virtue of the above-described acts, among others, Defendant AstraZeneca

knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1128. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1129. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the New York State Government to approve and pay such false and fraudulent claims.

1130. The New York State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1131. By reason of the Defendant's unlawful acts, the State of New York has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1132. The State of New York is entitled to the maximum penalty of \$12,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendant.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the New York False Claims Act provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that New York has sustained because of AstraZeneca's actions, plus a civil

penalty of not less than \$6,000 and not more than \$12,000 for each violation of N.Y. STATE FIN. LAW § 189;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant N.Y. STATE FIN. LAW § 119(6) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XIX

Louisiana Medical Assistance Programs Integrity Law Louisiana Rev. Stat. §437 *et seq.*

1133. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1134. This is a claim for treble damages and penalties against all Defendant on behalf of the State of Louisiana under the Louisiana Medical Assistance Programs Integrity Law, Louisiana Rev. Stat. §437 *et seq.*

1135. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1136. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Louisiana in extreme jeopardy. Had the State of Louisiana known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not

have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Louisiana— one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1137. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Louisiana – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1138. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1139. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1140. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1141. By virtue of the above-described acts, Defendant knowingly made, used, or Louisiana State Government to approve and pay such false and fraudulent claims.

1142. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Louisiana State Government to approve and pay such false and fraudulent claims.

1143. The Louisiana State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1144. By reason of the Defendant's unlawful acts, the State of Louisiana has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Louisiana Medical Integrity Programs Integrity Law that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount three times the amount of damages that Louisiana has sustained because of AstraZeneca's actions for violation of the Louisiana Medical Assistance Programs Integrity Law, Louisiana Rev. Stat. §437 *et seq.*;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant Louisiana Medical Assistance Programs Integrity Law, Louisiana Rev. Stat. §437 *et seq.* and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XX
Massachusetts False Claims Act
Massachusetts Gen. Laws c.12 §5(A)

1145. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1146. This is a claim for treble damages and penalties against the Defendant on behalf of the Commonwealth of Massachusetts under the Massachusetts False Claims Act, Massachusetts Gen. Laws c.12 §5(A).

1147. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1148. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the Commonwealth of Massachusetts in extreme jeopardy. Had the Commonwealth of Massachusetts known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine

two separate false claims were submitted to the Commonwealth of Massachusetts – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1149. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the Commonwealth of Massachusetts – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1150. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1151. By virtue of the above-described acts, among others, Defendant AstraZeneca

knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1152. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1153. By virtue of the above-described acts, Defendant knowingly made, used, or caused the Commonwealth of Massachusetts to approve and pay such false and fraudulent claims.

1154. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Commonwealth of Massachusetts to approve and pay such false and fraudulent claims.

1155. The Commonwealth of Massachusetts, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1156. By reason of the Defendant's unlawful acts, the Commonwealth of Massachusetts has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Massachusetts False Claims Act provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount three times the amount of damages that Massachusetts has sustained because of AstraZeneca's actions for violation of the Massachusetts False Claims Act, Massachusetts Gen. Laws c.12 §5(A);

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant Massachusetts False Claims Act, Massachusetts Gen. Laws c.12 §5(A) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XXI
City of Chicago False Claims Ordinance
Municipal Code of Chicago §1-22-010-§1-22-060

1157. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1158. This is a claim for treble damages and penalties against all Defendant on behalf of the City of Chicago under the Chicago False Claims Ordinance, Municipal Code of Chicago §1-22-010-§1-22-060.

1159. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1160. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place beneficiaries of the City of Chicago (employees, retirees of the City of Chicago and their respective dependents) in extreme jeopardy. Had the City of Chicago known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the

City of Chicago – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1161. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the City of Chicago – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1162. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the drug safety procedures the City relies upon, inclusive of drug interaction alerts, would have directed that such use was contraindicated and caused the City to refuse payment for such concomitant usage. Instead, drug safety procedures relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1163. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1164. By virtue of the above-described acts, among others, Defendant has knowingly

and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1165. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the Chicago City Government to approve and pay such false and fraudulent claims.

1166. The Chicago City Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1167. By reason of the Defendant's unlawful acts, the City of Chicago has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

COUNT XXII
New Jersey False Claims Act
N.J. STAT. §2A:32C-1-17

1168. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1169. This is a claim for treble damages and penalties against the Defendant on behalf of the State of New Jersey under the New Jersey False Claims Act N.J. STAT. §2A:32C-1-17.

1170. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1171. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of New Jersey in extreme jeopardy. Had the State of New Jersey known of

the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of New Jersey– one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1172. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of New Jersey – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1173. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false

information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1174. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1175. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1176. By virtue of the above-described acts, Defendant knowingly made, used, or cause the State of New Jersey to approve and pay such false and fraudulent claims.

1177. The State of New Jersey, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by Defendant, paid and continues to pay the claims that would not be paid but for Defendant's illegal inducements and/or business practices.

1178. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the State of New Jersey to approve and pay such false and fraudulent claims.

1179. By reason of the Defendant's unlawful acts, the State of New Jersey has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the New Jersey False Claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages

that the state of New Jersey has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of N.J. STAT. §2A:32C-1-17;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant N.J. STAT. §2A:32C-1-17 and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XXIII
Rhode Island's State False Claims Act
R.I. Gen. Laws § 9-1.1-1 – 9-1.1-8

1180. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1181. This is a claim for treble damages and penalties against the Defendant on behalf of the State of Rhode Island's False Claims Act R.I. Gen. Laws § 9-1.1-3.

1182. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1183. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Rhode Island in extreme jeopardy. Had the State of Rhode Island known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false

claims were submitted to the State of Rhode Island– one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1184. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Rhode Island– one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1185. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1186. By virtue of the above-described acts, among others, Defendant AstraZeneca

knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1187. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1188. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the State of Rhode Island to approve and pay such false and fraudulent claims.

1189. By virtue of the above-described acts, Defendant knowingly made, used, or cause the State of Rhode Island to approve and pay such false and fraudulent claims.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of Rhode Island's False Claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the state of Rhode Island has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of R.I. Gen. Laws § 9-1/1-3;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant R.I. Gen. Laws § 9-1.1-4(d) and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XXIV
Wisconsin's False Claims Act
Wis. Stat. § 20.931

1190. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1191. This is a claim for treble damages and penalties against the Defendant on behalf of the State of Wisconsin's False Claims Act Wis. Stat. § 20.931.

1192. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1193. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Wisconsin in extreme jeopardy. Had the State of Wisconsin known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Wisconsin— one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1194. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have

refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Wisconsin – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1195. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1196. By virtue of the above-described acts, among others, Defendant AstraZeneca did knowingly and willfully promote Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1197. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1198. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the State of Wisconsin to approve and pay such false and fraudulent claims.

1199. By virtue of the above-described acts, Defendant knowingly made, used, or cause the State of Wisconsin to approve and pay such false and fraudulent claims.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

- a. That by reason of the aforementioned violations of Wisconsin's False Claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the state of Wisconsin has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of Wis. Stat. § 20.931;
- b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant Wis. Stat. § 20.931 and/or any other applicable provision of law;
- c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and
- d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XXV
Oklahoma's False Claims Act
63 Okl. St. §5053-5053.7

1200. Plaintiff-Relator incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1201. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1202. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Oklahoma in extreme jeopardy. Had the State of Oklahoma known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote

prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Oklahoma— one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1203. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Oklahoma – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1204. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1205. By virtue of the above-described acts, among others, Defendant AstraZeneca

knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1206. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1207. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the State of Oklahoma to approve and pay such false and fraudulent claims.

1208. By virtue of the above-described acts, Defendant knowingly made, used, or cause the State of Oklahoma to approve and pay such false and fraudulent claims.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

- a. That by reason of the aforementioned violations of Oklahoma's False Claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the state of Oklahoma has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of 63 Okl. St. §5053.1.4;
- b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant 63 Okl. St. §5053.1.4 and/or any other applicable provision of law;
- c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and
- d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XXVI
North Carolina False Claims Act
N.C. Gen. Stat. § 1-605 – 618, §108A-63

1209. Relator-Plaintiff incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1210. This is a claim for treble damages and penalties against the Defendant on behalf of the State of North Carolina under the North Carolina False Claims Act N.C. Gen. Stat. § 1-605-618, §108A-63.

1211. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1212. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of North Carolina in extreme jeopardy. Had the State of North Carolina known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of North Carolina – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1213. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc

interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of North Carolina – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1214. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1215. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1216. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1217. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the State of North Carolina to approve and pay such false and fraudulent claims.

1218. By virtue of the above-described acts, Defendant knowingly made, used, or cause the State of North Carolina to approve and pay such false and fraudulent claims.

1219. By reason of the Defendant's unlawful acts, the State of North Carolina has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the North Carolina False Claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the state of North Carolina has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of N.C. Gen. Stat. § 1-605-618, §108A-63;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant the N.C. Gen. Stat. § 1-605-618, §108A-63 and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XXVII
Minnesota False Claims Act
Minn. Stat. § 15.C01 *et. seq*

1220. Relator-Plaintiff incorporates by reference and re-alleges all above paragraphs as if fully set forth herein.

1221. This is a claim for treble damages and penalties against the Defendant on behalf

of the State of Minnesota under the Minnesota False Claims Minn. Stat. § 15.C01 *et. seq.*

1222. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1223. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Minnesota in extreme jeopardy. Had the State of Minnesota known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Minnesota— one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1224. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were

submitted to the State of Minnesota – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1225. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1226. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1227. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1228. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the State of Minnesota to approve and pay such false and fraudulent claims.

1229. By virtue of the above-described acts, Defendant knowingly made, used, or cause the State of Minnesota to approve and pay such false and fraudulent claims.

1230. By reason of the Defendant's unlawful acts, the State of Minnesota has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

WHEREFORE, Plaintiff demands judgment against Defendant AstraZeneca as follows:

a. That by reason of the aforementioned violations of the Minnesota False Claims provisions that this Court enter judgment in Plaintiff's favor and against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the state of North Carolina has sustained because of AstraZeneca's actions, plus a civil penalty of not less than \$5,500 and not more than \$11,000 for each violation of Minn. Stat. § 15.C01 *et. seq*;

b. That Relator, as *Qui Tam* Plaintiff, be awarded the maximum amount allowed pursuant Minn. Stat. § 15.C01 *et. seq* and/or any other applicable provision of law;

c. That Relator be awarded all costs and expenses of this action, including attorney's fees and court costs incurred in the prosecution of this suit; and

d. That Plaintiff and Relator have such other and further relief that this Court deems just and proper.

COUNT XXVIII
Maryland False Health Claims Act of 2010
Subtitle 6, False Claims Against State Health Plans and
State Health Programs, §2-601 *et seq*.

1231. Plaintiff restates and incorporates each and every allegation above as if the same were fully set forth herein.

1232. This is a claim for treble damages and penalties under the Maryland False Health Claims Act of 2010, Subtitle 6.

1233. By virtue of the acts described above, defendants knowingly presented or caused to be presented, false or fraudulent claims to the Maryland State Government for payment or approval.

1234. By virtue of the acts described above, defendants knowingly made, used, or

caused to be made or used false records and statements, and omitted material facts, to induce the Maryland State Government to approve and pay such false and fraudulent claims.

1235. The Maryland State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by defendants, paid and continues to pay the claims that would not be paid but for defendants' illegal business practices.

1236. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR for off-label and dangerous uses from at least 1997 onwards.

1237. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Maryland in extreme jeopardy. Had the State of Maryland known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Maryland – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1238. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now

has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Maryland – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1239. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1240. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1241. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1242. By virtue of the above-described acts, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce the State of Maryland to approve and pay such false and fraudulent claims.

1243. By virtue of the above-described acts, Defendant knowingly made, used, or cause

the State of Maryland to approve and pay such false and fraudulent claims.

1244. By reason of the defendants' acts, the State of Maryland has been damaged, and continues to be damaged, in a substantial amount to be determined at trial.

1245. The State of Maryland is entitled to the maximum penalty of \$10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by defendants.

COUNT XXIX
Colorado Medicaid False Claims Act
C.R.S. § 25.5-4-304 *et seq.*

1246. Plaintiff restates and incorporates each and every allegation above as if the same were fully set forth herein.

1247. This is a claim for treble damages and civil penalties under the Colorado Medicaid False Claims Act C.R.S. § 25.5-4-304 *et seq.*

1248. The Colorado Medicaid False Claims Act C.R.S. § 25.5-4-304 *et seq.* provides for liability for *inter alia* any person who engages in any or all of the following conduct.

(a) Knowingly presents, or causes to be presented, to an officer or employee of the state a false or fraudulent claim for payment or approval;

(b) Knowingly makes, uses, or causes to be made or used a false record or statement material to a false or fraudulent claim;

(c) Has possession, custody, or control of property or money used, or to be used, by the state in connection with the "Colorado Medical Assistance Act" and knowingly delivers, or causes to be delivered, less than all of the money or property;

(d) Authorizes the making or delivery of a document certifying receipt of property used, or to be used, by the state in connection with the "Colorado Medical Assistance Act" and, intending to defraud the state, makes or delivers the receipt without completely knowing that the information on the receipt is true;

(e) Knowingly makes, uses, or causes to be made or used, a false record or statement material to an obligation to pay or transmit money or property to the state in connection with the

"Colorado Medical Assistance Act", or knowingly conceals or knowingly and improperly avoids or decreases an obligation to pay or transmit money or property to the state in connection with the "Colorado Medical Assistance Act";

(f) Conspires to commit a violation of paragraphs (a) to (e) of this subsection (1).

1249. By virtue of the conduct alleged herein, including the exchange of kickbacks and submissions of non-reimbursable claims described above, Defendants knowingly violated each of the above subsections of the Colorado Medicaid False Claims Act by and through their intentional and/or knowing violations of federal and state laws, including the Anti-Kickback Statute, as described herein.

1250. The Colorado Medicaid Program, unaware of the falsity or fraudulent nature of Defendant's illegal conduct, paid for claims that otherwise would not have been allowed.

1251. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Colorado in extreme jeopardy. Had the State of Colorado known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Colorado— one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1252. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc

interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Colorado – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1253. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1254. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1255. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1256. By reason of these improper payments, the Colorado Medicaid Program has been damaged, and continues to be damaged, in a substantial amount.

COUNT XXX
Connecticut Medicaid False Claims Act
CHAPTER 319v Sec. 17b-301a et seq.

1257. Plaintiff restates and incorporates each and every allegation above as if the same were fully set forth herein.

1258. This is a claim for treble damages and penalties under the Connecticut Medicaid False Claims Act CHAPTER 319v Sec. 17b-301a et seq.

1259. By virtue of the acts described above, Defendant knowingly presented or caused to be presented, to an officer or employee of the State of Connecticut, false or fraudulent claims for payment or approval under medical assistance programs administered by the Department of Social Services.

1260. By virtue of the acts described above, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to secure the payment or approval by the State of Connecticut false or fraudulent claims under medical assistance programs administered by the Department of Social Services.

1261. By virtue of the acts described above, Defendants conspired with each other and with others to defraud the State of Connecticut by securing the allowance or payment of a false or fraudulent claim under medical assistance programs administered by the Department of Social Services.

1262. The Connecticut State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by defendants, paid and continues to pay the claims that would not be paid but for Defendant illegal inducements and/or business practices.

1263. By reason of the Defendant acts, the State of Connecticut has been damaged, and

continues to be damaged, in substantial amount to be determined at trial.

1264. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Connecticut in extreme jeopardy. Had the State of Connecticut known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Connecticut – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1265. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Connecticut – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1266. Furthermore, if the label accurately reflected that the concomitant usage of

quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1267. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1268. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1269. The State of Connecticut is entitled to the maximum penalty of \$10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by the Defendant.

COUNT XXXI
Washington Medicaid False Claims Act

1270. Plaintiff restates and incorporates each and every allegation above as if the same were fully set forth herein.

1271. This is a claim for treble damages and penalties under the Washington Medicaid False Claims Act.

1272. By virtue of the acts described above, Defendant knowingly presented or caused to be presented, to an officer or employee of the State of Washington, false or fraudulent claims for payment or approval under medical assistance programs.

1273. By virtue of the acts described above, Defendant knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to secure the payment or approval by the State of Washington false or fraudulent claims under medical assistance programs.

1274. By virtue of the acts described above, Defendants conspired with each other and with others to defraud the State of Washington by securing the allowance or payment of a false or fraudulent claim under medical assistance programs.

1275. The Washington State Government, unaware of the falsity of the records, statements and claims made, used, presented or caused to be made, used or presented by defendants, paid and continues to pay the claims that would not be paid but for Defendant illegal inducements and/or business practices.

1276. By reason of the Defendant acts, the State of Washington has been damaged, and continues to be damaged, in substantial amount to be determined at trial.

1277. AstraZeneca's willful and reckless concealment of the dangerous consequences of using methadone concomitantly with quetiapine has placed and continues to place residents and citizens of the State of Washington in extreme jeopardy. Had the State of Washington known of the extreme danger presented by the concomitant use of methadone and quetiapine, it would not have approved payment for such concomitant usage. Accordingly, each time a physician wrote prescriptions for the concomitant use of methadone and quetiapine two separate false claims were submitted to the State of Washington – one for the methadone prescription and one for the quetiapine prescription. Furthermore, had pharmacists known of the extreme danger posed by this combination, they would have refused to fill concomitant prescriptions of methadone and quetiapine.

1278. AstraZeneca's willful and reckless decision not to amend the quetiapine labels when it had knowledge of quetiapine's deadly effect of prolonging the QTc interval caused physicians to use Seroquel concomitantly with drugs also associated with prolonging the QTc interval. If the label had been amended earlier to include the warning the quetiapine label now has concerning its use with QTc prolonging agents, physicians and pharmacists alike would have refused to either prescribe or fill quetiapine with drugs associated with prolonging the QTc interval. Accordingly, each time a physician wrote prescriptions for the concomitant use of quetiapine with a drug known to increase the QTc interval two separate false claims were submitted to the State of Washington – one for the drug known to cause increases in the QTc interval and one for the quetiapine prescription.

1279. Furthermore, if the label accurately reflected that the concomitant usage of quetiapine with another drug that increases the QTc interval should be avoided the State Drug Utilization Review Board would have directed that such use was contraindicated and refused payment for such concomitant usage without a prior authorization being approved by State Medicaid authorities. Instead, the State Drug Utilization Review Board relied on the false information disseminated by AZ that the concomitant use of quetiapine with another drug known to cause QTc prolongation was safe.

1280. By virtue of the above-described acts, among others, Defendant AstraZeneca knowingly and willfully promoted Seroquel and Seroquel XR and perhaps other pharmaceuticals for purposes not approved by the FDA.

1281. By virtue of the above-described acts, among others, Defendant has knowingly and willfully promoted Seroquel and Seroquel XR for dangerous and non-medically acceptable uses.

1282. The State of Washington is entitled to the maximum penalty of \$11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by defendants.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff-Relator Allison Zayas, plaintiffs United States, various States and Commonwealths and the City of Chicago pray for judgment against Defendant AstraZeneca as follows:

a. That Defendant be found to have violated and be enjoined from future violations of the Federal False Claims Act, 31 U.S.C. §3729 *et seq.*;

b. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the United States Government has sustained because of Defendant AstraZeneca's false or fraudulent claims, plus the maximum civil penalty for each violation of 31 U.S.C. §3729;

c. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of California has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not more than \$10,000 for each violation of CAL. GOV. CODE §12651(a)(3);

d. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of Delaware has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$11,000 for each violation of 6 DEL. CODE ANN. TIT. 6, §1201(a)(3);

e. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the District of Columbia has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of D.C. CODE ANN. §2-3-8.14(a)(3);

f. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of Florida has sustained because of

Defendant AstraZeneca's actions, plus a civil penalty of \$11,000 for each violation of FLA. STAT ANN. §68.082(2)(a)(3);

g. That this court enter judgment against Defendant AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages the state of Hawaii has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of HAW. REV. STAT. §661-21-(a)(3);

h. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of Illinois has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of 740 ILL. COMP. STAT. §175/3(a)(3);

i. That this court enter judgment against Defendant AstraZeneca in an amount equal to not less sustained because of AstraZeneca's actions, plus a civil penalty of not more than \$10,000 for each violation of the IND. CODE ANN. § 5-11-5.5-2;

j. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of Louisiana has sustained because of Defendant AstraZeneca's actions, plus a civil penalty to the full amount Defendant unjustly received as a result of unlawful conduct for violating Louisiana Medical Assistance Programs Integrity Law, Louisiana Rev. Stat. §437 *et seq.*;

k. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the Commonwealth of Massachusetts has sustained because of Defendant AstraZeneca's actions, plus a civil penalty to the full amount Defendant unjustly received as a result of unlawful conduct for violating Massachusetts False Claims Act, Massachusetts Gen. Laws c.12 §5(A);

l. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of Michigan has sustained because of Defendant AstraZeneca's actions, plus a civil penalty to the full amount Defendant unjustly received as a result of unlawful conduct for violating MICH. COMP LAWS § 400.603, 606 and 607;

m. That this Court enter judgment against Defendant AstraZeneca against AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the State of Montana has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not more than \$10,000 for each violation of the MONT. CODE ANN § 17-8-403;

n. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of New Hampshire has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for violation of N.H. REV. STAT. ANN. §167:61-b;

o. That this court enter judgment in Plaintiff's favor and against Defendant AstraZeneca in an amount three times the amount of damages that the State of New Mexico has sustained because of Defendant AstraZeneca's actions for violation of N.M. STAT. ANN. § 27-14-4;

p. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of Nevada has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of NEV. REV. STAT. ANN. §357.014(1)(c);

q. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the City of Chicago has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of the Chicago False Claims Ordinance;

r. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of Tennessee has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of the Tennessee Medicaid False Claims Act;

s. That this Court enter judgment against Defendant AstraZeneca in an amount equal to the damages that the state of Texas has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$15,000 for each violation of TEX. HUM. RES. CODE ANN. § 36.002(8) that results in injury to an elderly person, a disabled person, or a person younger than 18 years of age, or not less than \$1,000 and not more than \$10,000 for each violation of TEX. HUM. RES. CODE ANN. § 36.002(8) that does not result in an injury to a person;

t. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the Commonwealth of Virginia has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of Va. Code Ann. §8.01-216.3(a)(1), (2);

u. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of Georgia has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of GA. CODE 49-4-168.1;

v. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of Indiana has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 for each violation of IND. CODE ANN. §5-11-5.5-2;

w. That this Court enter judgment against Defendant AstraZeneca in an amount equal to three times the amount of damages the State of New York has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$6,000 and not more than \$12,000 for each violation of N.Y. STATE FIN. LAW §189;

x. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the State of New Jersey has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of N.J. STAT. §2A:32C-1-17;

y. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the State of Rhode Island has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of R.I. Gen. § 9-1.1-1 – 9-1.1-8;

z. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the State of Wisconsin has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of Wis. Stat. § 20.931

aa. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the State of Oklahoma has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of 63 Okl. St. § 5053-5053.7;

bb. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the State of North Carolina has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of N.C. Gen. Stat. § 1-605-618, §108A-63;

cc. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the state of Minnesota has sustained because of Defendant AstraZeneca's actions, plus a civil penalty of not less than \$5,000 and not more than \$10,000 for each violation of Minn. Stat. § 15C.01 *et. seq.*;

dd. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than two times and not more than three times the amount of damages that the state of Colorado sustained because of Defendant AstraZeneca's actions;

ee. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than \$10,000 for each and every false or fraudulent claim that the state of Connecticut sustained because of Defendant AstraZeneca's actions;

ff. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than \$10,000 for each and every false or fraudulent claim that the state of Maryland sustained because of Defendant AstraZeneca's actions;

gg. That this Court enter judgment against Defendant AstraZeneca in an amount equal to not less than \$11,000 for each and every false or fraudulent claim that the state of Washington sustained because of AstraZeneca's actions;

hh. That Plaintiff-Relator be awarded the maximum amount allowed pursuant to §3730(d) of the Federal False Claims Act, and the equivalent provisions of the state statutes set forth above;

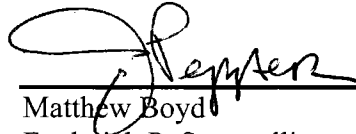
ii. That Plaintiff-Relator be awarded all costs of this action, including attorneys' fees and expenses; and

jj. That Plaintiff-Relator recover such other relief as the Court deems just and proper or that is necessary to make Plaintiff-Relator whole.

Demand for Jury Trial

Pursuant to Rule 38 of the Federal Rules of Civil Procedure, Plaintiff hereby demands a trial by jury.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Matthew Boyd", is written over a solid horizontal line.

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